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HEREDITY, ENVIRONMENT, AND EVOLUTION
TH. DOBZHANSKY

THE ROLE OF LIPIDS AND LIPOPROTEINS IN ATHEROSCLEROSIS
JOHN W. GOFMAN *ET AL.*

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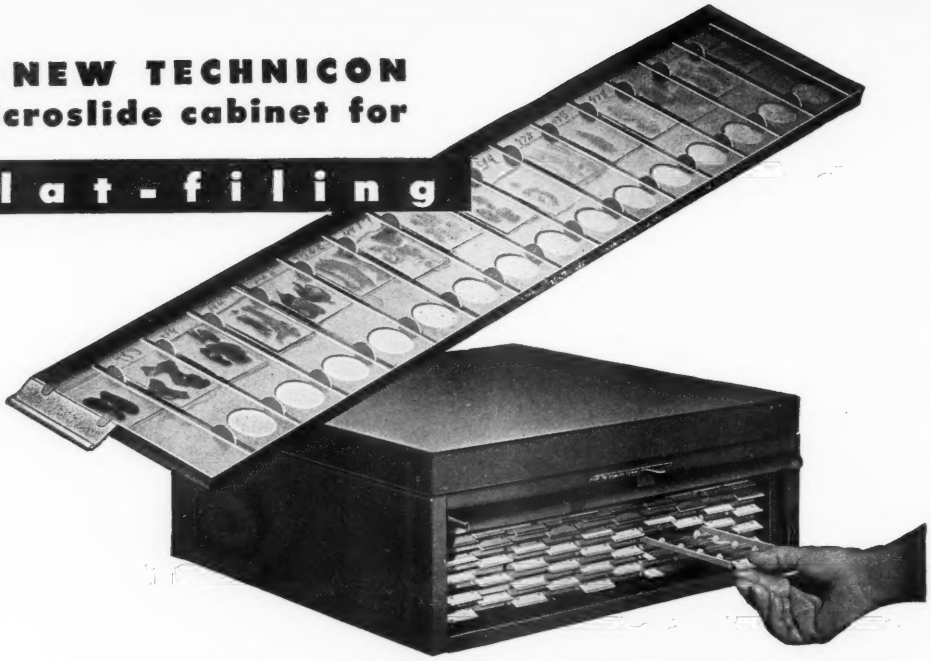

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Heredity, Environment, and Evolution

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THE SAVAGE ONSLAUGHT on genetics by Lysenko and his partisans has had one useful result—and only one—that is, a great intensification of interest in genetics and evolution, not only among scientists but among educated people in general. Therefore, this is a propitious time for an attempt to restate some of the basic concepts of modern genetics and of evolution theory. It goes without saying that these concepts differ from those current in the past, and it is a safe prediction that they will continue to evolve unless the sciences of genetics and evolution are destroyed everywhere as they have been in Russia. Furthermore, the concepts vary somewhat, although to a minor extent, from one geneticist to another. The responsibility for the formulations offered here rests, of course, with the writer.

Genetics has been defined by Bateson as a study "of the phenomena of heredity and variation; in other words . . . the physiology of descent." Heredity, variation, and descent are aspects of the same basic phenomenon, although superficially they may seem distinct or even antagonistic. It is a matter of observation that children resemble parents, and this resemblance is ascribed to heredity. The resemblance is, however, not absolute, either between parents and children or among sibs. This is called variation. When we find, through observation or inference, that the organisms living now came from ancestors different from them we speak of evolution or descent.

A man may resemble his mother in some respects or "traits," his father in other traits, and be unlike either in still others. It looks as if what is inherited is not a general likeness but rather resemblance in different particular traits. In common as well as in scientific parlance, such human traits as skin color, eye color, hair form, and head shape are considered hereditary. No abstruse analysis is needed, however, to show that a "trait" is merely an abstraction useful for purposes of description, and as such cannot be inherited. An individual arises from the union of an egg contributed by the mother with a spermatozoon contributed by the father. These sex cells have no eyes, no hair, and no skin color. But a fertilized egg does develop, by means of a long series of very complex transformations and through many successive stages, into an organism which has eyes of a certain color, hair of a certain form, a more or less pigmented skin, etc. Furthermore, the traits or characteristics of an individual organism at any stage of its development are related to, and are to a certain extent predictable from, a knowledge of the traits of its parents and other ancestors. It is evident that what is inherited is a dynamic pattern of developmental processes which charts the course of the transformations of the body from fertilization to birth, to adulthood, and to death.

This charting, however, does not amount to anything like complete determinism. It is well known that the course of development is influenced by the environment. Therefore the outcome of development at any stage is a function of both the heredity of the developing individual and the environment in which the process has taken place. Heredity does not determine traits; it determines, according to the somewhat awkward expression proposed by the Danish biologist Raunkaier, the "norm of reaction" of the organism to the environment.

Different environments evoke different reactions in organisms with similar heredities; different heredities engender different reactions in organisms which develop in similar environments. It is therefore obviously necessary to distinguish the outcome of development from its cause. Johannsen proposed to designate the former as the *phenotype* and the latter as the *genotype*. The phenotype comprises all external and internal structures and functions of the organism. It can be studied and described by morphological, anatomical, and physiological methods. The genotype of an individual is the sum total of its hereditary properties. Examination of the pedigree, or of the progeny, or both, is needed to study the genotype. The phenotype of an individual changes continuously as the development proceeds, and, in fact, never becomes fixed. A series of photographs of a person taken at different times, from birth to maturity, old age, and death, illustrates the changeability of the phenotype. The genotype is relatively stable; the nature of this stability will be discussed.

It is a widespread misapprehension that hereditary traits are independent of the environment, and that traits subject to environmental modification are *ipso facto* not hereditary. On the contrary, no organic form or function can develop except as a response of a certain genotype to a certain environment. The so-

called "nature-nurture" (genotype-environment) problem is not to distinguish which traits are genotypic and which are environmental, for all traits are genotypic and environmental. The problem is to what extent the actually observed variability in individuals of a species (such as man) is caused by the available variety of genotypes, and by the existing variety of environments. In this sense, the relative importance of genotype and of environment is quite different for different traits. For example, the blood group to which a man belongs seems to be fixed by his heredity; no method of changing the blood antigens is known at present. The skin color depends both on the genotype and on the exposure of the skin to a certain part of the ultraviolet spectrum. Man's behavior is supposed to conform to circumstances, i.e., to the environment. But it is easy to show that behavior is influenced also by the genotype. For example, a man with a black skin (a genotypic trait) will, in a "color conscious" society (environment), evince a different behavior (phenotype) from a man with a light skin. The fact that in different social environments these men's behavior might be alike, or reversed, does not make the behavior independent of the genotype.

The relative importance of genotype and of environment in the determination of the developmental pattern is not unalterable. If the environment becomes standardized, the variability of genotypes increases in importance. Environmental agents become more influential when they grow stronger or more diversified, or when the organisms on which they act are genotypically uniform or nearly so. Now, man creates new environments and is therefore potentially able to augment or diminish the rigidity of genotypic determination. It is clear that the development of an individual is an orderly sequence of physiological and, ultimately, physicochemical reactions in which the genotype and the environment are involved. If a detailed knowledge of these reactions were available, the phenotype would be under our control to a much greater extent that it is now. As Goldschmidt has pointed out, any change in the phenotype produced by a variation of the genotype could, in principle, be produced by environmental influences as well. Although this presupposes a more nearly perfect knowledge of development than is actually available, the principle is valid. Medical treatment of hereditary disease or, indeed, of any other disease consists essentially in placing the patient in environments so contrived that his genotype reacts by engendering a phenotype which is regarded as desirable. Medicine and pedagogy are, from the standpoint of genetics, sciences of management of the human phenotype. Heredity is often spoken of as "destiny." It is destiny largely in proportion to our biological ignorance.

The foremost problem of genetics has been to investigate the structure and the operation of the genotype in individual and in evolutionary development. To date, the greatest discovery in this field has been that made by Mendel. Mendel demonstrated that the genotype is not a diffuse continuum, which it was believed to be before Mendel (the "blood" theory of heredity), but a sum of discrete particles, now called genes. The rules of the transmission of genes from parents to offspring have been established by means of a certain powerful analytical tool, invented by Mendel and perfected by his successors. This tool is hybridization of varieties of plants or animals which differ in some known respects; the distribution in the offspring of the traits in which the parents differed is followed one by one, and is recorded quantitatively. The rules discovered by Mendel enable biologists to make sense of a great mass of otherwise chaotic data; they also enable geneticists to devise new experiments and to predict their outcome. The gene theory has been established without the genes' having been seen under the microscope, just as chemical reactions have been understood in terms of molecules and atoms without molecules and atoms' having been seen.

The next step was made by the combined efforts of many brilliant men, among whom Weismann and Morgan were most important. This was the demonstration that the genes, or most of them, are carried in the microscopically visible chromosomes. The gene ceased to be merely a symbol; it became also a material particle. But the structure and the method of action of the gene still remained conjectural. The next advance, due again to collective achievement of numerous workers, among whom Muller has been most prominent, is now in process of accomplishment. Although many loose parts of the story still remain to be tied together, it seems most probable that the gene is a single molecule of nucleoprotein, or a part of a supermolecule, the chromosome. Some genes occur, however, in the cytoplasm also. There has developed, moreover, a most intriguing zone transitional between, first, cytoplasmic genes, which are necessary parts of a cell of a given species, second, viruslike symbionts which may or may not be present, and, finally, parasitic viruses which are transmitted from individual to individual not by heredity but by infection. A chromosome proves to be not a fortuitous assemblage of independent genes, but an organized system; the precise nature of the interrelations of the genes carried in the same chromosome is, however, still problematic. Whatever it may prove to be, heredity is a process enacted primarily on a molecular level inside the cells, and secondarily magnified to those macroscopic dimensions in which we are accustomed to observe the outcome of heredity.

A human egg cell is estimated to weigh about one millionth of a gram. The increase in weight from egg to adult is, accordingly, some fifty billion fold. The source of the material for this enormous growth is not far to seek. It is the food and water consumed and assimilated by the organism. The development of any organism involves, then, transformation of materials withdrawn from the environment into a likeness of the assimilating organism and of its ancestors. Heredity is a process whereby the organism reproduces itself by consuming a part of its environment. This is especially obvious when we observe living things giving rise to progeny. But self-reproduction takes place in any living body. Experiments with isotopes have shown an amazing lack of permanence of most of the adult mammalian body; many body constituents are periodically broken down and reconstructed anew from food materials. Heredity is, fundamentally, self-reproduction.

The units of self-reproduction are genes. Construction of their own copies is the most important and possibly the only function which the genes perform. Just what the chemical processes are whereby a copy of a gene appears next to it is unknown. It is possible that a gene first synthesizes its negative image, which next gives rise to a positive. Or the gene molecule may undergo transformations whose end result is two such molecules. In any case, the process of self-reproduction may be symbolized thus:

$$A + B = 2A + C$$

where A is the gene, B the materials from which the copy is made, and C the by-products or waste products. The essence of the process is that two gene molecules are formed where only one was present before. Whatever the chemistry may prove to be, the process is cyclic, and it is this cyclic nature that makes heredity possible.

The allegation that geneticists regard the genes as isolated from the rest of the body and from the environment is absurd. It has been known for about half a century that the chromosomes, and hence the genes, are reduplicated between the consecutive cell divisions. The genes are probably chemically the most active cell constituents. The genes change all the time, but the basic fact is that the changes are cyclic: they lead to self-reproduction. This is the modern meaning of the Weismannian distinction—which has been misinterpreted by geneticists as well as by philosophers—between the germ plasm and the somatoplasm. The germ plasm is the genic materials which reproduce themselves; the somatoplasm is produced in the process of gene self-reproduction. The "stability" of the genes is peculiarly dynamic—they change to produce their own copies. Self-reproduction is the fundamental quality of life that distinguishes it from inanimate nature. This explains the apparently paradoxical nature of life: life changes the environment and is changed by the environment, and yet it preserves an inner continuity which is, in fact, its basic property.

Every organism can exist in a certain range of environments and can subsist on a certain range of food materials. This means that a gene, A, is able to reproduce itself not only from a material, B, but also from other materials, denoted B^1, B^2, B^3, etc. The results of the self-reproducing processes are, then:

$$A + B^1 = 2A + C^1$$
$$A + B^2 = 2A + C^2$$
$$A + B^3 = 2A + C^3.$$

In other words, with rare exceptions, a gene either forms a faithful copy of itself or fails to reproduce altogether. Variations in the environment give variations in the products (phenotypes) C^1, C^2, C^3, etc., and not in gene A. This accounts for the paradox of variability of the phenotype and stability of the genotype which makes heredity possible. The so-called acquired characters are not inherited because the phenotype, C, is a product of the reproduction of the genotype, A, and not vice versa.

The genes are, nevertheless, not unchangeable. In fact, they can be changed quite readily: The genic materials can be burned, or we can poison the genes. Since the chemical basis of the genes is in all likelihood nucleoprotein, they should be capable of undergoing many kinds of changes. The problem is not whether genes can be changed but what is the outcome of a change. It seems that the property of the gene-molecule which makes self-reproduction possible is based on some as yet unknown chemical structure which can be lost very easily. By way of analogy, one can say that a gene is a very delicate mechanism, random changes in which are more likely to spoil it than to permit its continued functioning, and far more likely to spoil it than to improve it.

As a consequence, three kinds of changes in the genes can be visualized: (1) Changes that make the gene unable to reproduce itself. Such a gene is no longer a gene; it is dead. This is doubtless the most frequent kind of change, which leads to losses of genes. (2) Changes that permit self-reproduction to occur, but that are not incorporated in the reproduction process. In other words, the copy formed is like the original, or ancestral gene structure, and not like the new one. Such changes are ephemeral, and are not detected by genetic methods. They do not infringe upon the dynamic stability of the gene as it has been defined here. Stanley was able to produce and to demonstrate such changes in the tobacco virus by

chemical methods. (3) Changes that allow self-reproduction to continue and that are reproduced, or copied, in the daughter genes. Such changes are permanent and stable, in the same sense in which the ancestral gene structure was called stable. These are the mutations of genetics.

Several environmental agents that speed up the mutation process are known: x-rays, ultraviolet radiation, high temperature, and certain chemicals. The effects of these agents are, however, unspecific, in the sense that they enhance the probability of occurrence of mutations of all kinds (although not necessarily to the same extent). In the last analysis, every mutation is caused by environmental influences, and there is no theoretical reason why geneticists could not eventually learn to induce at will specific mutations in specific genes. Such a feat may already be within our grasp in the type transformation of pneumococcus bacteria. But the interpretation of these transformations is not yet quite clear and, undeniably, complete control of the mutation process is still not in sight.

The relations between mutations and the environment will now be considered from a different point of view—that of relative reproductive efficiency of the unchanged and mutated genes, and of organisms carrying them. We have seen that a gene encroaches on the environment and transforms a part of it (food) into copies of itself. The efficiency of this process may be described in terms of the number of copies (progeny) created per unit of time. The greater the surviving progeny of an organism, the better this organism may be said to be adapted to a certain environment. The process of differential perpetuation of different genes and genotypes is Darwinian natural selection. With respect to adaptedness, or fitness, three types of mutations may be distinguished.

(1) The adaptedness of the mutant is lower than that of the ancestral form in all existing or attainable environments. If a mutant leaves fewer surviving descendants per unit of time than does the ancestral form, the number of individuals of the former will decrease relative to the number of the latter. No matter how small may be the disadvantage of the mutant, the end result of the process will usually be extinction of the mutant. Inasmuch as the outcome of selection is in this case elimination of the mutant and preservation of the orginal type of gene or organism, this form of selection is a conservative force. It has been called by Schmalhausen "stabilizing selection," because it preserves the existing type of organization.

(2) The adaptedness of the mutant is higher than that of the ancestral form in all environments the species occupies or can reach. The outcome of the process of natural selection will here be the converse of the preceding case: the ancestral type will become extinct, and the environment will be monopolized by the mutant. An evolutionary change will have taken place, because a previously existent type is replaced by a new one.

(3) The adaptedness of the mutant is higher than that of the ancestral type in some environments, but lower in other environments. The process of natural selection will in this case lead to elimination of neither the mutant nor the original type. Instead, the outcome of selection will be establishment of an equilibrium state, at which both the old and the new types of organization will continue to exist. The numbers and relative frequencies of the two types will depend upon the abundance of the two kinds of environments in the world and upon the absolute reproductive efficiencies of the two types of organisms involved. The outcome of natural selection will thus be a diversification of the organisms existing in the universe. Two types will occur where only one lived before the change took place. This is the dynamic form of natural selection.

Evolution of living matter is compounded of changes of the kinds just described. Evolution is utilitarian in the sense that organisms change in the process of becoming adapted to their environments. The adaptation is brought about by natural selection which, in turn, is the outcome of differential perpetuation of different genotypes. Differential perpetuation is often styled "competition" and "struggle for life." Both expressions are metaphors, and have often been misconstrued. Imagine two species of bacteria or two genetic types of the same species of bacteria which multiply in the same test tube with nutrient broth. They are "competing" with each other in the sense that the more food one of them consumes, the less is left for the other. But the bacteria do not devour each other. When two species or varieties of grass occur in the same meadow they "struggle" with each other, in the sense that there is only a limited amount of space available for their growth. But this struggle does not involve anything like fighting in the human sense. *Competition* and *struggle* are emotionally loaded words, which are best avoided in discussions of causes of evolution.

No less misleading is the expression "survival of the fittest," which Herbert Spencer unfortunately coined to describe the operation of natural selection, and which became associated with something like the image of the Nietzschean superman. Now, *fitness* in the evolutionary sense, or *adaptive value*, as it is better called, does not necessarily connote even a superior ability of an individual to survive, and a lack of fitness in this sense is not synonymous with weakness or frailty. A superior adaptive value of one genotype over an-

other simply means that the carriers of the former leave, on the average, more surviving progeny than do the carriers of another genotype in the same environment. This superiority may result from the fact that individuals of one genetic type are stronger and more resistant to environmental hazards, and live longer than individuals of other genetic types. Or one type may be more sexually active or more fecund than another. Individual vigor and fecundity are not necessarily correlated, and a superior fecundity may compensate or even overcompensate for deficient vigor. This has indeed been observed in an experiment of the writer on some *Drosophila* flies, in which natural selection favored the spread of a type actually inferior to another type in viability between the egg and the adult stage, the second type being discriminated against by natural selection.

The processes of mutation and natural selection have been described here as though they involved changes of individual genes. This may be strictly true only in some viruses, which have been styled "naked genes" because they seem to consist of a single molecular species. In organisms other than viruses, the genotype is an integrated system of many kinds ("loci") of genes. Estimates of the numbers of gene loci in higher organisms are of the order of thousands or tens of thousands. Most or all of these loci change from time to time by mutation, and are represented in populations of a species by different variants ("alleles"). The constellation of gene alleles that an individual has consists of genes it has inherited from its ancestors or acquired by mutation of the inherited genes. The genes do not determine parts of the body, organs, traits, or even independent physiological processes. The entire genotypic system defines the matrix of the development of the organism as a whole. The development is apparently epigenetic, not preformistic, although preformism appeals to the thinking of many biologists, and many overtly or covertly preformistic theories are still current in biology. In any case, it is generally agreed that the adaptive value of a genotype in an environment is a property of the genotype as a whole, and not a simple sum of the values of its constituent genes. A gene, A, may be deleterious in combination with B, neutral with C, and useful with D.

Mendel showed that the variety of genotypes created in the process of sexual reproduction is staggeringly great. If a species has n genes, each represented by X variants (alleles), the number of genotypes possible in such species is X^n. With n of the order even as low as 1000, the number of possible genotypes is immense. Sexual reproduction is an unbelievably efficient trial and error mechanism because it creates countless new genotypes to be tested by natural selection. Because of the high efficiency of sex in the performance of this biological function, sexual reproduction has become established in most organisms as the normal method of propagation. Natural selection has evolved and perfected sex because it proved to be a basic adaptation which makes other adaptations more readily available. One of the most ridiculous features of the "dialectical" theory of Lysenko is his belief that the magic of sex "invigorates" the organism; his rejection of the gene theory has landed Lysenko in primitive animism. He fails to understand that it is the relative stability of genes that makes life possible, but that the stability is combined with a remarkable freedom in the creation of new genotypes in the process of sexual reproduction. The conservatism of heredity is balanced by the creativeness of sex.

The relationships between environment and evolution are subtle enough to make them often misunderstood. Evolution is controlled by the environment on two levels, and yet the environment cannot be said to impose changes on living species. The first level is that of mutation. The second is that of natural selection. The most accurate, although metaphorical, way of describing the dependence between evolution and environment is to say that environment provides the challenges to which organisms may or may not respond by adaptive modifications.

Mutations are, in the last analysis, physicochemical alterations in the genes or chromosomes; hence they cannot be wholly independent of the environment. And yet mutations are described as random and undirected changes. These adjectives mean that mutations arise regardless of whether or not the organism needs them for purposes of adaptation, and irrespective of whether the change may or may not be useful in some existing or possible environment. To suppose otherwise is to believe in magic. But the kinds of mutation that occur in any one gene are a function of the structure of that gene. Now, every gene is a product of a historical development extending from the dawn of life to our day. This development has been under the control of natural selection, hence of the environment. The structure of a gene is a distillate of its history, and the mutations that may occur in a gene are determined by the succession of environments in which that gene and its ancestors existed since the beginnings of life. The environment prevailing at the time mutation takes place is only a component of the environmental complex that determines the mutation.

Between the occurrence of mutation and the realization of an evolutionary change in a living population is interposed the domain of processes of population dynamics. The most important process in that domain is natural selection. The superiority of one genotype over others in adaptedness is clearly a func-

tion of the environment in which the process of selection is enacted. Nevertheless, natural selection involves a unique kind of interaction between the organism and the environment, the outcome of which depends upon both interacting variables. Similar environments therefore do not necessarily produce similar organic types. For example, deserts in different parts of the world are inhabited by many remarkably parallel adaptive types of animals and plants. The similarity of cacti in American deserts and certain euphorbias in South Africa is impressive. And yet, some of these adaptive types are missing in some deserts where the environment seems propitious for them. Their absence in appropriate environments is really no more surprising than the fact that human civilizations which have developed in similar environments are so often different. Organic evolution, like the genesis and development of human civilizations, is irreversible and unrepeatable. In the case of organic evolution, we now begin to discern the reason for this. A mutation is, in general, reversible and recurrent; in other words, the gene A mutates from time to time to a, but a mutates back to A with an equal or different frequency. If the gene A is adaptive in summer, for example, and a adaptive in winter, the selection favoring A during one season may be undone during the next season. But when many genes have mutated, and when natural selection has established a new and harmonious genotype including these mutants, the probability of reversion or of repetition of the process becomes negligible. Evolution becomes irreversible and unrepeatable as it ceases to be a physiological process and becomes a historical process.

Based on an address read before the joint meeting of Section L of the American Association for the Advancement of Science, the American Philosophical Association, and the Philosophy of Science Association, on December 30, 1949, in New York City.

The Role of Lipids and Lipoproteins in Atherosclerosis

John W. Gofman, Frank Lindgren, Harold Elliott, William Mantz, John Hewitt, Beverly Strisower, and Virgil Herring

Division of Medical Physics, Donner Laboratory, and the *Radiation Laboratory, University of California,*[1] *Berkeley,* and

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ATHEROSCLEROSIS is generally considered to be the major disease of this era. Its consequences in the coronary, cerebral, and peripheral arteries, in the form of occlusive phenomena, are responsible for more death and disability than any other disease. In spite of much study and research there is still no agreement concerning the sequence of pathogenetic events, etiology, or treatment of atherosclerosis. The not-too-rare occurrence of coronary artery occlusions (almost always a consequence of atherosclerosis) in young men from 20 to 40 years of age testifies to the fallacy of the idea, still prevalent, that atherosclerosis is a problem of the aged or senile. For the male it is a real threat in the prime of life. The absence of the disease at autopsy in many persons who have survived to be octogenarians is eloquent evidence that atherosclerosis should be regarded as a disease and not as an inevitable consequence of aging.

For many years it has been known that cholesterol (and its esters), phospholipids, and fatty acids are prominent components of early atheromatous lesions, whereas secondary pathological processes supervening may alter the relative preponderance of certain of these substances in late lesions. Some workers have indicted exogenous (dietary) cholesterol for the production of the disease, while others have denied the significance of this source of cholesterol, on the basis that large quantities of cholesterol may be endogenously synthesized from such precursors as water and acetate. The suggestion has also been made that atherosclerosis is the result of the chylomicronemia which follows meals. No agreement has been in sight,

[1] This work was supported (in part) by the Atomic Energy Commission and the United States Public Health Service. The authors wish to acknowledge with gratitude the generous and invaluable advice and assistance given by Profs. Hardin B. Jones and John H. Lawrence.

largely because no objective means for the evaluation of conflicting ideas has been available.

In any effort to formulate a concept of this disease process one must take cognizance of certain well-established clinical and experimental observations and determine whether a new concept is in harmony with such observations. We shall describe briefly several pertinent features of atherosclerosis and then attempt to show that our experiments and the ideas we have evolved therefrom do provide a reasonable picture of some aspects of this disease.

A. Blood cholesterol levels. Myriad determinations of blood cholesterol levels have been made by workers all over the world in an effort to show whether or not the blood cholesterol (free or esterified) is elevated in those patients who develop atherosclerosis. The result remains highly controversial. Some workers claim a significant elevation in blood cholesterol level for a majority of patients with atherosclerosis, whereas others debate this finding vigorously. Certainly a tremendous number of people who suffer from the consequences of atherosclerosis show blood cholesterols in the accepted normal range. There does exist a group of disease states (including diabetes mellitus, nephrotic nephritis, severe hypothyroidism, and essential familial hypercholesteremia) in which the blood cholesterol level may be appreciably elevated. Such patients do show, in general, earlier and more severe atherosclerosis than the population at large. Yet no bridge has been established between this relatively small group and the vast population of individuals with normal blood cholesterols from which the majority of victims of atherosclerotic disease are drawn.

B. Experimental atherosclerosis in the rabbit. Anitschkow (*1*) demonstrated that cholesterol feeding in the rabbit results in the production of hypercholesteremia and of a lesion in the arteries greatly resembling the human atherosclerotic lesions. Controversy has existed in the literature since Anitschkow's work, criticism of the significance of his experiments having centered largely around the fact that the rabbit is herbivorous and hence ordinarily ingests essentially no cholesterol. It is our opinion that pertinent clues to the human problem are obtainable from cholesterol-induced atherosclerosis in the rabbit. We shall endeavor to detail the observations and ideas on which this opinion is based below.

C. Incidence of atherosclerosis in humans. The common medical knowledge that the incidence of atherosclerosis, its severity, and its complications increase, in general, with age must be accounted for in any over-all concept of this disease. This must be done while still reckoning with the observations that severe atherosclerosis may be seen in young individuals, especially males, and that at autopsy many persons of all age groups may be free of atherosclerosis. Another unexplained but striking fact is the occurrence of coronary artery occlusions (secondary to atherosclerosis) in males far more frequently than in females, this differential being most pronounced in the age group below 40 years and decreasing steadily with increasing age above 40 years.

It is reasonably certain that the variation in analytical blood cholesterol levels in the groups just discussed fall far short of affording an adequate explanation of the facts regarding incidence of the disease.

D. Occurrence of atherosclerosis in association with diabetes mellitus. As a group, diabetic patients are more susceptible to early and severe atherosclerosis than is the population in general. It has been stated by authorities on diabetes that atherosclerosis and its complications represent the major problems facing diabetics now that insulin is available to prevent fatalities due to the diabetes itself. Hypercholesteremia alone does not account for the extraordinary susceptibility of diabetics to atherosclerosis.

Some two years ago the present group of authors undertook a physicochemical investigation of those giant molecules of serum which may be composed of cholesterol, its esters, phospholipids, fatty acids, and protein as building blocks. The basic premise was that it is entirely possible that a defect might exist in certain of these giant molecules, which could be responsible for the development of atherosclerosis, whereas the mere analytical levels of any of the building blocks in serum might be of little or no significance. Thus, in a sense, it would not necessarily be any more logical to study the total level of serum cholesterol if we are interested in a particular molecule containing cholesterol than it would be to study serum alanine or glycine levels if it were serum albumin about which we are concerned. The instrument we found to be of greatest service in this research has been the preparative and analytical ultracentrifuge (Spinco Model E). Gofman, Lindgren, and Elliott (*3*) and Lindgren, Elliott, Gofman, and Strisower (*4*) have explained the ultracentrifugal situation with respect to the lipids and lipoproteins of rabbit and human serum and have shown how the ultracentrifuge may be used to characterize certain physicochemical properties of these components in the native state. Our subsequent work has revealed that a considerable diversity of components exists in the low density group heretofore known as the B_1-lipoprotein. Since the research with rabbit atherosclerosis gave us pertinent leads with respect to the human problem, this aspect of the work will be described first.

Rabbit Atherosclerosis

Serum lipid and lipoprotein changes. Normal rabbits (*4*) show a lipoprotein of hydrated density 1.03 g/ml in their serum. This lipoprotein contains approximately 30 percent cholesterol[2] by weight. Ultracentrifugally it appears as a single component of flotation rate between 5 and 8 Svedberg units under our specified conditions.[3]

On feeding rabbits three grams of cholesterol per week a highly interesting sequence of events occurs, which we believe has a direct bearing on the development of atherosclerosis in these animals. The initial increment in serum cholesterol during the feeding is manifested by an increase in the concentration of the previously existing 5–8 S_f component. The level of this component may increase as much as fourfold. In other rabbits, however, following the initial increase in level of the 5–8 S_f component, a series of new cholesterol-bearing giant molecules appear in the serum, including several detectable components, of S_f class 10–30 (in some cases components of even higher S_f values appear). Meanwhile, as these new components develop the level of the 5–8 S_f molecule is maintained at an approximately constant value, the serum cholesterol increment thereafter being essentially all in the form of the molecules of higher S_f values. Any particular rabbit may show any number (from none to all) of the new components, in spite of the fact that this animal receives the same maintenance ration of cholesterol as do all the other animals. Sera or sodium chloride solutions containing high concentrations of the molecules just described scatter light intensely (are turbid). This is worthy of note, since many authors erroneously attribute the turbidity to the presence of chylomicrons. In fact, at no time in the course of cholesterol feeding is a large fraction of the cholesterol in rabbit serum transported in the form of chylomicrons. The literature reports (*2, 5*) which indicate that chylomicrons contain cholesterol may be in error because the methods of obtaining the chylomicron fraction for analysis would allow considerable contamination with the much lower molecular weight molecules we have described in this section.

The new components that appear in rabbit serum with cholesterol feeding are differentiable by their flotation rates, and in addition by virtue of the fact that their hydrated densities are 1.01 and less, in contrast to the value 1.03 for the molecules of the 5–8 S_f class.

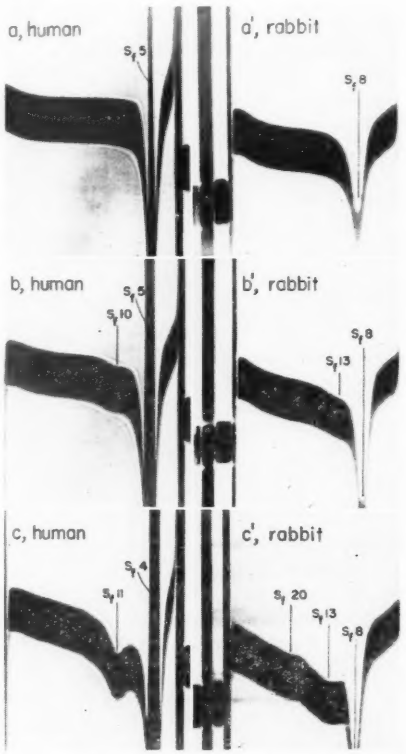

FIG. 1. Ultracentrifugal flotation diagrams of lipids and lipoproteins of the human and rabbit. The normal rabbit (1a′) shows only a lipoprotein of the S_f 5–8 class, but during cholesterol induction of atherosclerosis develops additional components of the S_f 10–30 class (1b′ and 1c′). The human may show only a single lipoprotein of the 3–8 S_f class (1a), or components of the S_f 10–20 class may be present in variable degree (1b and 1c). The vertical bar through the main inverse peak in (1a, 1b, and 1c) represents a region of refractive index gradient in the cell so great that an entering light beam is thrown out of the optical system. The presence of this bar does not interfere with the resolution of the S_f 10–20 components. All analytical runs were made at a rotor speed of 52,640 rpm in a cell of 0.8-cc capacity.

[2] All analytical cholesterol determinations were made by the method of Schoenheimer and Sperry.

[3] In referring to molecules that move against a centrifugal field (as they do when they are of lower density than that of the medium in which they are dissolved) we shall speak of *flotation*, instead of using the more cumbersome term, *negative sedimentation*. The Svedberg unit (1 S equals 10^{-13} cm/sec/dyne/g) will be used. Thus a molecule described as having a flotation rate of 20 S units under our specified conditions will be referred to as a molecule of the 20 S_f class, etc. All the runs reported here were made at a temperature of 27° ± 2° C in a sodium chloride solution of density 1.0625 (unless otherwise stated), using low density substances previously isolated by differential preparative ultracentrifugation. Flotation rates have not been converted to a value corresponding to the $S_{20,w}$ value of sedimentation runs, since we feel it may ultimately prove more valuable to retain the data in the form obtained rather than to add much unnecessary calculation and back calculation. No conclusions reported here will be influenced by corrections for concentration, viscosity changes due to slight temperature difference between runs or by the Ogston-Johnston effect, since such corrections are outside the range involved in our considerations.

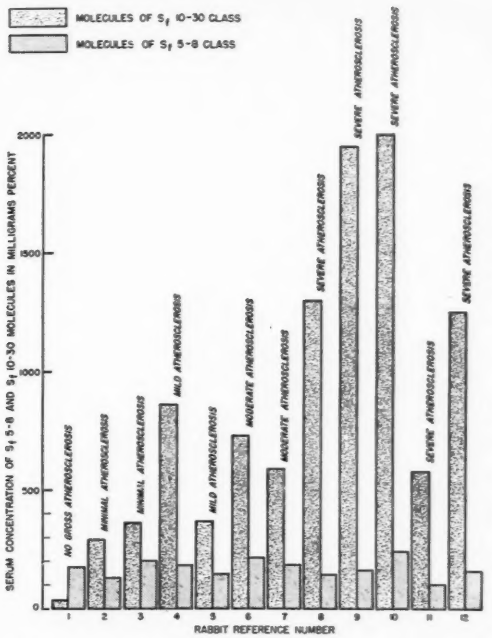

FIG. 2. Plot showing the relationship of severity of atherosclerosis (as determined by autopsy) to the concentration of S_f 5–8 and S_f 10–30 classes of molecules. Each number (plotted horizontally) refers to an individual rabbit.

The entire group of rabbits was autopsied after 15 weeks of cholesterol feeding. It was found that those rabbits failing to develop high levels of the components of S_f greater than 5–8 units showed no gross atherosclerosis or showed minimal atherosclerosis, whereas mild to severe atherosclerosis developed in those with high concentrations of the molecules of the S_f 10–30 class (see Figs. 1 and 2). From the observation that all the rabbits attained comparable levels of the 5–8 S_f component but showed widely varying degrees of atherosclerosis one can suggest that probably this component is not a guilty one. On the other hand, the correlation between the development of severe atherosclerosis and the presence in blood of high concentrations of components of the S_f 10–30 class suggests that at least some of these components either are the molecules which deposit in atheromatous plaques or are a reflection in the blood of the metabolic abnormality which results in cholesterol-induced atherosclerosis. Direct evidence as to the deposition of these molecules in plaques is now being obtained by a combination of the ultracentrifugal approach with labeling of the various lipid and lipoprotein components, with P^{32} incorporated into the phospholipid and H^3 incorporated into the cholesterol.

Components of S_f greater than 8 S do not appear in serum until 30–40 days after the initiation of cholesterol feeding and, further, such components do not appear in appreciable concentration until the total serum cholesterol has reached approximately 200–250 milligrams percent. It has been known a long time that experimental rabbit atherosclerosis shows a "latent" period of about 40 days after initiation of feeding and that atherosclerosis is rare or minimal in experiments of this duration in rabbits whose total serum cholesterols never rise above 250 mg%. The correlation between our observations and the older data lends further plausibility to the suggestion that the molecules of the S_f 10–30 class are those intimately involved in the production of atherosclerosis.

One point is worth noting with respect to the size of these molecules. Flotation rates higher than 8 S_f do not infer that the components moving with such rates are of higher molecular weight than the 8 S_f molecules. For two molecules of density 1.00 and 1.03 floating in a medium of density 1.06, there will be approximately a twofold difference in flotation rates with no difference in molecular weights, assuming identical shape factors. The shape factors and molecular weights are now being determined upon isolated ultracentrifugal components from rabbit serum by the supplementary study of their diffusion and viscometric properties.

Human Atherosclerosis

In parallel with the studies of rabbit hypercholesteremia and atherosclerosis an investigation of the types of low density molecules present in human serum has been carried on, including those present in individuals with and without known atherosclerotic disease. It was of course obvious to search for possible similarities in the mechanism of cholesterol transport in the human on feeding ad libitum and in the rabbit fed cholesterol. The correlation between the findings in the human and the rabbit appear even more extensive than might have been hoped for and enable us to present a somewhat unified concept of certain aspects of the nature of atherosclerosis in both species.

There are present in the isolated low density group of molecules from many human sera components of flotation rate (under our specified conditions) greater than 70 S, which may correspond to the class of chylomicrons, and in addition, components of hydrated densities less than 1.00 whose flotation rates are between 40 and 70 S units. These components are markedly influenced by the relationship between the time of drawing the blood samples and the time and character of previous meals. For the present discussion of atherosclerosis no further reference will be

made to these components. There is also present in every one of some 600 sera studied at least one low density lipoprotein, of S_f value between 3 and 8 units (the S_f of this component varies from individual to individual), the hydrated density of which is in the range 1.03–1.04 g/ml. Over short periods (a few days) the level of this component and its properties appear uninfluenced by previous meals.

In addition to the components just described, there are present in some sera, but *not* in all sera, low density lipid and lipoprotein components, containing cholesterol, with flotation rates (under our specified conditions) in the S_f 10–20 class (see Fig. 1). These components are easily differentiated from those constituting part of the lipemia of meals. It has been possible to show by runs of flotation versus density of medium that the components of higher S_f values are of lower hydrated densities than the major low density molecules of the 3–8 S_f class. By differential ultracentrifugation in solutions of graded density, we have been able to isolate the individual molecular species in a state of reasonable ultracentrifugal homogeneity and to do some studies of chemical composition. Molecules in the S_f 10–20 class contain approximately 30 percent cholesterol by weight, but contain little or no protein, in contrast to the major low density group of 3–8 S_f class, which show a protein content of 25 percent by weight.

Study of several groups of individuals with respect to the presence of molecules of the S_f 10–20 class indicates that the presence of these molecules in the serum of humans is related to the development of atherosclerosis. The following groups of individuals have been investigated:

a. Young women without known disease, from 20 to 40 years of age.

b. Young men without known disease, from 20 to 40 years of age.

c. Women without known disease, from 40 to 70 years of age.

d. Men without known disease, from 40 to 70 years of age.

e. Diabetic females without additional known disease, from 25 to 70 years of age.

f. Diabetic males without additional known disease, from 35 to 70 years of age.

g. Female patients with a proved myocardial infarction, from 50 to 70 years of age.

h. Male patients with a proved myocardial infarction, from 30 to 70 years of age.

Since more than 95 percent of myocardial infarctions occur in individuals whose coronary arteries are atherosclerotic, a group of patients who have had an unequivocal episode of this type should represent excellent material for the evaluation of the significance of S_f 10–20 molecules with respect to atherosclerosis. To preclude the criticism that metabolic upsets during

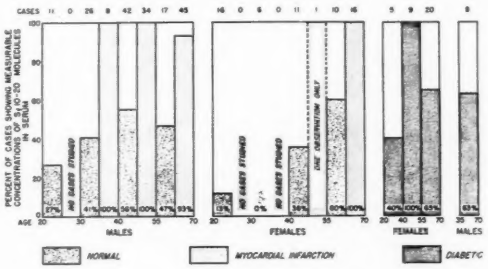

FIG. 3. The above histograms indicate the percentages of cases showing measurable concentrations of S_f 10–20 molecules in serum by age, sex, and history of myocardial infarction or diabetes mellitus. Males and females without known disease are compared with proved myocardial infarctions by age increments of 20–29, 30–39, 40–54, and 55 to 70 years inclusive. The frequencies of these molecular types in diabetic group are presented by the ages of 20–39, 40–54, and 55–70 years for females and 35–70 years in the small sample of diabetic males. "No cases studied" is used to denote that no myocardial infarctions in the particular age categories involved were available.

the period of recovery from an acute infarction might alter the picture, or that any drug therapy might do the same, no cases were studied unless the infarction had occurred at least six weeks before blood was drawn for study. The criteria required for inclusion in this group were (a) a typical clinical history of a myocardial infarction, (b) typical laboratory findings during the episode, and (c) electrocardiographic changes characteristic of myocardial infarction. Patients in borderline categories with respect to any of the criteria were excluded. Patients with myocardial infarction and coexistent hypertension were excluded in the effort, for the present, to eliminate any obscuring of the data by the hypertensive state. In all, 104 patients with myocardial infarctions, including 87 males and 17 females, were chosen for this study.

The data in Figs. 3 and 4 summarize all the findings for all of the groups examined with respect to the presence and concentration of molecules of the S_f 10–20 class. The following conclusions are drawn from these data:

a. The incidence of measurable concentrations of molecules of the S_f 10–20 class is significantly higher in males from 20 to 40 years of age than in females of the same age group. Assuming that these S_f 10–20 molecules reflect the metabolic disturbance which results in atherosclerosis, these data are in accord with the fact that females of this age group are much less likely to show significant atherosclerosis than are the corresponding males.

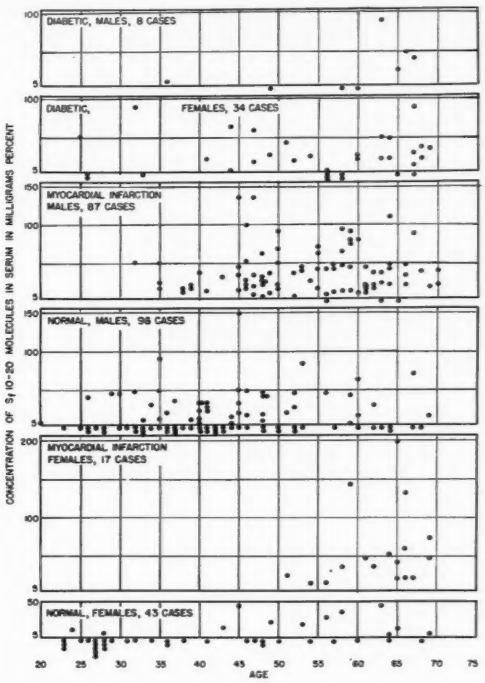

FIG. 4. Presented by scatter diagram are concentrations of S_f 10–20 molecules in individual cases grouped by physiological categories. Selection of bloods for analysis have been limited to 20–70 years in order to increase the numbers that could be studied in this age span. The limit of resolution, 5 milligrams percent, has been drawn and those determinations that are essentially "zero" are placed below this limit. No concentrations of these S_f 10–20 molecules were found present below the measured concentration of 7.5 milligrams percent.

b. In the age group over 40 years, normal males and females both show significant increases in the incidence of measurable concentrations of molecules of the S_f 10–20 class as compared with the corresponding younger age groups. Further, the differential between the sexes in the older age group is lessened compared with that in the younger age group. These observations are both consistent with the clinical observations that atherosclerosis increases in frequency with age in both sexes, and that the differential decreases with increasing age.

c. The data indicate a probably higher incidence of measurable concentrations of molecules of the S_f 10–20 class in diabetics than in the normals of the corresponding age groups. However, in certain of the diabetic categories larger numbers of cases will be helpful in establishing significance.

d. One hundred and one out of 104 patients with proved myocardial infarction show the presence of molecules in the S_f 10–20 class in measurable concentration. This would be fully anticipated if the S_f 10–20 class of molecules is directly related to the development of atherosclerosis.

The observation that approximately 50 percent of presumably normal individuals in the age group over 40 years show appreciable concentrations of S_f 10–20 molecules in their serum is expected from known pathological data (*6*), which indicate that approximately half the people in this age group are developing atherosclerosis, even though the disease is not clinically evident. The same type of reasoning holds for the other groups studied, including the diabetics.

In the rabbit, components analogous in many respects to the S_f 10–20 class of molecules of humans appear in serum as the result of dietary overloading with cholesterol. It was of interest, therefore, to know whether the dietary cholesterol intake might alter the level of concentration of the S_f 10–20 molecules in persons whose serum contained them. Our preliminary study of a group of 20 patients whose diet we have restricted in cholesterol and fats has demonstrated that the concentration of the S_f 10–20 class of molecules is definitely reduced or even brought down to a level below resolution ultracentrifugally in 17 of the cases studied within two weeks to one month.

The relationship between serum cholesterol levels and the presence of S_f 10–20 molecules in serum. As mentioned earlier, analytical blood cholesterol levels have proved highly unsatisfactory as a measure reflecting the occurrence or progress of atherosclerosis. We believe that our data may indicate the reason for this. A comparison of blood cholesterol levels as determined analytically (Schoenheimer-Sperry method) with the presence or absence of molecules of the S_f 10–20 class reveals that, although there is a general trend toward increased frequency of occurrence of such molecules in sera with cholesterols over 200 mg%, this is by no means a universal finding. It is quite common, also, to find sera with cholesterol levels well below 200 mg% with appreciable or high concentration of molecules of the S_f 10–20 class. In fact, several sera studied with cholesterol levels between 120 and 140 mg% show appreciable concentrations of these molecules. Further, it is common to find sera with cholesterol levels well over 200 mg% cholesterol without showing any measurable concentration of the S_f 10–20 class of molecules. At a particular cholesterol level one person may show 25 percent of the total serum cholesterol in the form of S_f 10–20 molecules, whereas another person may show essentially none in this form. It should also be noted that the

(*Continued on page 186.*)

Technical Papers

On Projection as a Possible Source of Apparent Color in Sunspots

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That sunspots occasionally show definite colors is a fact attested by numerous observers dating back at least to Messier (*4*), who in 1759 reported a deep brown color in the notable sunspot of that year. Many competent observers, however, have not conceded the objectivity of the observed colors and have ascribed them to illusions or to the secondary spectrum of objectives (*5*). The difficulty has been to account for them within the framework of accepted physical theories of the sun's constitution.

However the reconciliation is to be accomplished, such colors may be seen with reflectors as easily as with refractors, which fact greatly weakens the argument that they arise through the effects of the secondary spectrum. Moreover, two facts seem to suggest most strongly that some, if not all, of the observed colors are truly objective: 1) they are seen chiefly during maximum sunspot periods and are generally confined to the largest and most active class of spots; and 2) they are comparatively rare. Thus, of 6,169 individual sunspots observed by the writer at Baltimore in 1948, only 22 were found to be colored. It is not easy to see why, if the colors are illusionary, they should not be seen much more frequently.

Hitherto, the writer has been inclined to regard sunspot colors as being due to radiation from the spot in selective wavelengths (*1*); but while this may account for umbral colors, it is not easy to assign such a cause when the color is in the penumbra.

D. H. Menzel, in a letter to the writer referred to by Bartlett (*2*), suggests that color may also be due to the projection of chromospheric eruptions. A recent observation by the writer tends to confirm this view very strongly.

August 21, 1949, at 17h 24m, the writer observed a very large, irregular sunspot of F-1 type (Waldemeier classification) close to the equator in the northern hemisphere and almost on the solar meridian. The time given here is the mean time of observation, i.e., the mean of the sum resulting from the addition of the time when the observation began to the time when it ended. Actual times are given as follows:

At 17h 10m the penumbra was found to be normally grayish with little contrast. The umbra was certainly black. At 17h 29m the penumbra was observed to be red-violet and the umbra appeared brown. At 17h 32m the penumbra suddenly became a bright red-violet, showing marked contrast with the photosphere. At 17h 36m the penumbra was again grayish with little contrast and the umbra again looked black. Between 17h 32m and 17h 36m color in the penumbra was observed to fade and brighten alternately several times.

Although the writer had never seen this particular phenomenon before, it had been previously reported to him by at least two other observers on the writer's granulation program; and Walter L. Moore, observing with the 12.5-in. Clark reflector of the University of Louisville, had also reported colored areas in penumbrae, though the color had not been observed to fluctuate.

While observing this phenomenon, it occurred to the writer that the appearances corresponded very well to what might be expected from the passage over the spot of a chromospheric area of varying density—hence the fluctuations—in brightness inferior to the photosphere but superior to the penumbra and umbra. Thus, Menzel's suggestion of color by chromospheric projection appears to receive observational support.

In this connection an observation recently made at Climax may perhaps be confirmatory. In October 1948, the writer observed rapid changes of color (not merely fadings and darkenings) and other phenomena in a large sunspot. A telegram was sent to Walter Orr Roberts in charge of the High Altitude Observatory of Harvard at Climax, urging spectroscopic examination of this spot. In a letter to the writer (*3*), Roberts reported marked phenomena "directly over the region of the sunspot" and presumably within the chromosphere. There was also observed a brilliant emission in the yellow at the coronal line 5694 A. Since this activity took place above the spot, and therefore had a relatively dark background for projection, it seems quite possible that color effects might have been noticed which seemed to be in the spot itself.

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The Frequency of Beat of Sperm Tails

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Since Bidder (*1*) in 1895 estimated the vibrational frequency of choanocyte flagella, several methods of measuring the rate of ciliary beats have been devised, and a number of readings have been made on vibratile parts of protozoa, molluscs, vertebrates, and arthropods. Bidder's first approximation placed the rate at about 10 beats per sec, but he later (*2*) recorded 5 beats per sec in *Grantia*, giving at the same time the opinion that a healthy frequency ought to be closer to 20 beats per sec. Gray (*3*) measured beats of cilia and flagella, ranging

from 5 per min for *Noctiluca* to 1200 for a sponge choanocyte, though the lower frequency has been questioned by Lowndes (*10*). Gray (*4, 5*), using a mechanical stroboscope combined with a motion picture camera, later established a rate of 5–16 vibrations per sec in cilia from the gills of the mussel. An electric spark of a duration less than 0.0001 sec was used with a shutterless camera by Jennison and Bunker (*7*) to record movement of the cilia of clam gills. Hammond (*6*) measured the beat of cilia of several protozoa by means of a shuttered stroboscope and found, at 20°–24° C, a range from 6 or 8 per sec for *Vorticella* up to 42 per sec for *Stentor*. Lucas and Douglas (*11*) by direct observation with continuous light counted 2.2–5.2 beats per sec in cilia of a turtle's trachea. Lowndes (*8–10*) photographed moving flagella with a high speed motion picture camera which exposed 60 frames a sec with an exposure of 1/8000 sec, and recorded frequencies of about 7–12 beats per sec in several flagellates. Pease and Kitching (*12*), in a study of the effects of hydrostatic pressure on ciliary speed, used a variable speed, slotted, rotating disk similar to that used by most previous investigators. They reported that the cilia of mussel gills generally beat between 600 and 700 times per min. Except for Lowndes (*8*), who studied the sperms of an ostracod, apparently no investigator has measured the rate of flagellar vibration of sperms.

In the present study, human sperms were mounted in spermatic fluid at a temperature of 32° C and observed in dark field, illuminated by stroboscopic light.[1] The instrument used furnishes an intense light of very short duration, and can be simply and instantly regulated to produce flashes from 600 to 14,500 times per min. If the frequency of the flashes is the same as the frequency of the beat of the tail, one apparently motionless tail is visible. If the frequency of the flashes is twice that of the tail, there are apparently two tails. If the flash frequency is half that of the tail, then again one tail appears, but this rate will not be confused with the rate which obtains when flash and tail frequencies are the same if one bears in mind that, in the latter case, doubling of the flash frequency produces a double tail image.

Unlike most flagellated cells, the sperm cell does not move forward at a steady rate. Further, the tail does not beat with a simple harmonic motion. The sperm progresses in irregular jerks, each burst of speed lasting less than a second. It is during the moment of greater speed that the frequency of the vibrating tail can be determined, while between spurts of speed, the cell moves more slowly and the beat of the tail is so slow that I could not measure it stroboscopically. There is no perfectly rhythmic alternation of the periods of slow and fast beat, nor is there complete uniformity of behavior from cell to cell. Many cells cannot be "stopped" with stroboscopic light because they seem to be altering their speed so often that it is impossible to tune in on any frequency. The lowest flash frequency at which a single image could be observed was 14–16 per sec. With 25–28 flashes per sec, visibility improved because flickering was minimized, but during the moments when the tails were "stopped" they appeared double, due to the fact that the light was flashing twice during each period of vibration. The figures given are the extremes of a number of readings. That the double frequency is not exactly twice the single is probably due partly to inaccuracy of the method and partly to the fact that different cells were used for each reading, since I was not able to follow any single sperm long enough to make two readings on it.

It is interesting to find that the tails of human sperm cells have a frequency of beat which is rather close to that of the cilia or flagella of clam gills or monads; but such a result is to be expected, since, in spite of the fact that these various cells are far separated in organic history, they are still of so much the same order of magnitude that the surprise would have come if they had proved to move at radically different speeds.

[1] General Radio Company, Cambridge, Massachusetts.

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Action of Carboxypeptidase Toward Peptides Containing Unnatural Aromatic Amino Acids[1]

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Since β-2-thienylalanine has been found to inhibit the growth of certain organisms through interference with the metabolism of its analogue, phenylalanine (*2, 3*), it seemed of interest to prepare peptides containing this and other unnatural aromatic amino acids, and to determine whether these peptide analogues would be antagonistic to the action of isolated proteolytic enzyme systems, as well as to the growth of microorganisms.

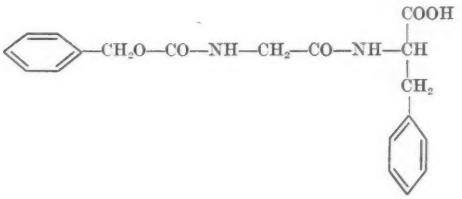
Carboxypeptidase from beef pancreas was selected as the enzyme to use in this study because it displays maximum activity toward substrates derived from aromatic amino acids, and because it can be isolated readily in pure form. Carbobenzoxyglycylphenylalanine (I) is hydrolyzed by carboxypeptidase more readily than any other synthetic peptide, and its racemate has been suggested as

[1] This work was supported in part by a research contract with the Office of Naval Research.

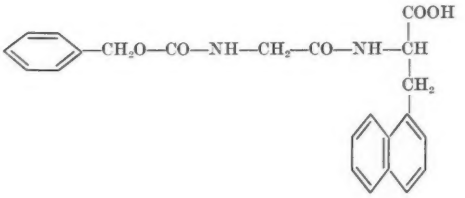
[2] Predoctorate Research Fellow, United States Public Health Service; on leave from Abilene Christian College, Abilene, Texas.

a standard for measurement of carboxypeptidase activity (*5*). Therefore, the compounds herein reported were fashioned after this peptide, and differ from it only by replacement of the benzene ring with other aromatic rings.

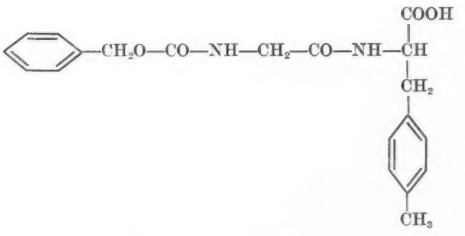
The following compounds have been synthesized in racemic form: carbobenzoxyglycyl-β-2-thienylalanine (II), carbobenzoxyglycyl-β-1-naphthylalanine (III), carbobenzoxyglycyl-β-2-naphthylalanine (IV), and carbobenzoxyglycyl-*p*-methylphenylalanine (V). At this time we wish to report the action of carboxypeptidase toward each of these compounds; the syntheses will be reported elsewhere.



Carbobenzoxyglycylphenylalanine (I)



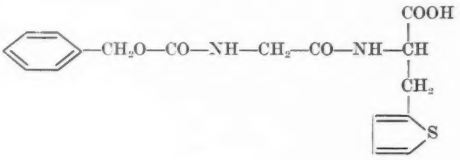
Carbobenzoxyglycyl-β-1-naphthylalanine (III)



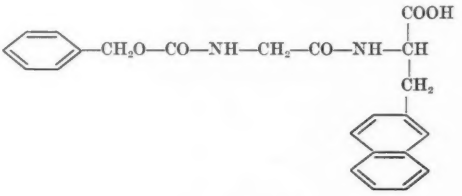
Carbobenzoxyglycyl-*para*-methylphenylalanine (V)

Table 1 lists the results of the hydrolytic studies. From these data it is possible to conclude the following: compounds (III) and (IV), containing the large naphthalene ring system, are quite resistant to hydrolysis; compound (II), containing the thiophene ring, is hydrolyzed at about one-half the rate of its benzene analogue, according to the initial velocity constants; compound (V), containing the *p*-methylphenyl group, is hydrolyzed about as readily by carboxypeptidase as is the typical substrate (I) in which the phenyl group is unsubstituted.

Stahmann *et al.* (*6*) found that certain peptides which resisted hydrolysis would inhibit the hydrolysis of a typical substrate when present in equimolar amounts. The data presented in Table 2 show the inhibitory effect of carbobenzoxyglycyl-β-2-naphthylalanine (IV) added in equimolar amounts to carbobenzoxyglycylphenylalanine (I). Simultaneous hydrolysis was carried out on (I) and



Carbobenzoxyglycyl-β-2-thienylalanine (II)



Carbobenzoxyglycyl-β-2-naphthylalanine (IV)

(IV) separately, under the same conditions, for comparison.

The carboxypeptidase used in this work was prepared by the method described by Anson (*1*). The enzyme concentrations given are based upon the rate of hydrolysis of racemic carbobenzoxyglycylphenylalanine (*5*). Each hydrolytic study was carried out in the following typical manner: 178 mg racemic carbobenzoxyglycylphenylalanine was suspended in 2 ml phosphate buffer, pH 7.6, and solution was effected by making distinctly pink to phenolphthalein with 1 *N* NaOH. The pH was reduced by the addition of 0.5 *N* acetic acid until the pink color just disappeared. The proper amount of enzyme suspension was added and the volume diluted to 5 ml. A 1-ml sample for the blank was immediately withdrawn and added to 9 ml of absolute alcohol, then reserved for subsequent titration. Hydrolysis was carried out at 37° C. The rate of hydrolysis was determined by titration of 1-ml samples by the alcohol titration method of Grassman and Heyde (*4*), using *N*/100 NaOH, with phenolphthalein as the indicator. The substrate concentrations were in each case 0.10 mM of the racemic compound per ml; the percent hydrolysis was calculated on the basis of the concentration of the L-isomer.

TABLE 1

RATE OF HYDROLYSIS OF SYNTHETIC PEPTIDES BY CARBOXYPEPTIDASE

Substrate	Enzyme concn. 10^{-4} mg N/ml	Time min	Hydrolysis %	Velocity constant, K^* 10^{-3} min^{-1}
Carbobenzoxyglycylphenylalanine (I)	1.5	70	27	1.9
		140	50	2.1
	2.7	30	17	2.6
		60	46	4.4
		120	63	3.3
Carbobenzoxyglycyl-β-2-thienylalanine (II)	1.5	70	13	0.9
		140	19	0.6
		255	31	0.6
Carbobenzoxyglycyl-β-1-naphthylalanine (III)	2.7	30	0	
		60	2	
		130	2	
	7.0	25	0	
		135	2	
Carbobenzoxyglycyl-β-2-naphthylalanine (IV)	3.4	30	1	
		90	6	
		8 hr	11	
	13.6	23	2	
		70	9	
Carbobenzoxyglycyl-p-methylphenylalanine (V)	2.7	30	17	2.6
		60	25	2.0
		130	52	2.4

$$* K = \frac{1}{\text{min}} \log_{10} \frac{100}{100 - \%\ \text{hydrolysis}}.$$

TABLE 2

INHIBITION OF HYDROLYSIS OF CARBOBENZOXYGLYCYLPHENYLALANINE BY CARBOBENZOXYGLYCYL-β-2-NAPHTHYLALANINE

Substrate	Enzyme concn. 10^{-4} mg N/ml	Time min	Hydrolysis %
Carbobenzoxyglycylphenylalanine	13.6	23	63
		70	73
		17 hr	79
Carbobenzoxyglycylphenylalanine plus carbobenzoxyglycyl-β-2-naphthylalanine	13.6	23	15
		70	54
		17 hr	75
Carbobeazoxyglycyl-β-2-naphthylalanine	13.6	23	2
		70	9

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Uptake of Radioactive Iodine by the Thyroids of Underfed Rats[1, 2]

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Thyroid activity in rats is depressed during starvation, an effect which has been attributed to a decrease in thyrotrophic function by the anterior pituitary (*3, 4*). From a quantitative aspect, a recent report from this laboratory on the effects of thiouracil on the thyroids of starved rats and mice indicated that the decrease in thyroid activity may be directly proportional to the reduced body weight of these animals (*1*). In other words, thyroid activity appeared to remain unchanged in starved rats when computed on a body weight basis.

We decided to test this finding further by administering radioactive iodine to starved rats and comparing their thyroid uptake with that of controls fed ad libitum.

TABLE 1

EFFECTS OF UNDERFEEDING ON SURVIVAL, GROWTH, AND THYROID WEIGHTS OF RATS

Group	Orig. No. per group	Final No. per group	Avg orig. body wt in g	Avg final body wt in g	Avg thyroid wt in mg	Avg thyroid wt/100-g body wt in mg
Controls, fed ad lib.	10	10	147.0	169.5	13.79	8.13 ±* 0.29
Fed ¾ ad lib. .	10	10	146.6	148.5	10.34	7.00 ± 0.42
Fed ½ ad lib. .	10	10	145.5	126.6	8.97	7.07 ± 0.55
Fed ¼ ad lib. .	10	8	145.4	111.0	8.60	7.71 ± 0.23
No feed	10	4	146.0	87.0	7.20	8.24 ± 0.52

* Standard error of mean.

Fifty young female rats of the Sherman strain, weighing approximately 145 g each, were divided into five groups of ten each and were started on ad libitum, ¾, ½, ¼, and no-feed regimens. The ¾, ½, and ¼ feed-allowanee levels were computed from the daily ad libitum feed consumption of the control group. The ration consisted of ground Purina Laboratory Chow. All rats were maintained in an air-conditioned room at a temperature of 75° F.

The unfed group was sacrificed at the end of 7 days, and the other four groups at the end of 14 days. Eight hours prior to sacrifice, each rat was injected intraperitoneally with 0.2 ml of carrier-free I^{131} (radioactive) estimated to contain approximately 2 μc. The thyroid of each sacrificed rat was removed, immediately weighed on a Roller-Smith balance and placed on the center of a

[1] Published with the approval of the Director of the Michigan Agricultural Experiment Station as Journal Article No. 1071.

[2] This study was aided in part by a grant from the U. S. Atomic Energy Commission.

[3] The authors wish to express their thanks to J. O. Reed and C. C. Lee for technical assistance and statistical analysis of the data.

small copper disk for counting. After allowing the thyroids to dry thoroughly, each was counted separately with a thin mica (1.55 mg/cm²) end window counter.

The data given in Table 1 show the expected effects of underfeeding on loss in body weight, the most severe weight losses occurring on the ¼ and no-feed regimens. In these two groups, only eight and four rats, respectively, survived out of an original number of ten each. Thyroid weight was reduced in all the underfed groups, but remained relatively unchanged on the basis of a 100-g body weight. This confirms a previous report from this laboratory on the effects of underfeeding on thyroid weight in rats (*2*).

The amounts of radioactive iodine taken up by the thyroids of each group of rats are given in Table 2. It

TABLE 2

EFFECTS OF UNDERFEEDING ON UPTAKE OF I^{131} BY THE THYROIDS

Group	Avg uptake of I^{131} per thyroid %	Radioactivity in counts per sec		
		Avg No. counts per thyroid	Avg No. counts per mg thyroid	Avg No. counts per thyroid / 100-g body wt
Controls fed ad lib.	7.9	20.05 ± 1.52*	1.50 ± 0.17*	12.01 ± 1.13*
Fed ¾ ad lib. .	6.1	16.71 ± 1.64	1.62 ± 0.15	11.28 ± 1.07
Fed ½ ad lib. .	5.0	13.26 ± 1.32	1.51 ± 0.14	10.52 ± 1.03
Fed ¼ ad lib. .	4.1	10.51 ± 1.00	1.28 ± 0.18	9.75 ± 1.27
No feed	3.2	8.92 ± 0.39	1.30 ± 0.08	10.23 ± 0.57

* Standard error of mean.

can be seen that the greatest amount of iodine, 7.9%, was taken up by the thyroids of the group fed ad libitum and progressively smaller amounts were taken up by the thyroids of the underfed groups. This was further shown in the actual number of counts obtained from the thyroids of each group of rats. The average number of counts per mg of thyroid tissue remained the same in all groups, indicating that underfeeding did not affect the concentration of iodine within the thyroids. On the basis of 100-g body weight, the counts per thyroid were similar in all the groups, showing that the amount of radioactive iodine taken up by each of the underfed groups was directly proportional to body weight.

It is well known that the thyroids of animals on diets deficient in iodine but otherwise adequate show a greater affinity for administered iodine than animals on iodine-adequate diets. To what extent the rats in this experiment were deficient in iodine as a result of underfeeding is unknown. However, these data support the conclusion that the primary effect of underfeeding is to reduce thyroid activity, and this effect is sufficient to overcome any increased affinity for iodine the thyroids may possess as a result of a possible deficiency in iodine intake.

These data are believed to constitute further proof of the hypothesis that the reduction in thyroid activity during starvation in rats is directly proportional to the reduced body weight of these animals. Whether these data would apply to rats during longer periods of starvation, or to rats of other age groups, cannot be answered at the present time.

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Amide Constituents of Tobacco Mosaic Virus Protein

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The possible presence of amides in tobacco mosaic virus protein has received little attention, although considerable work (*2–3*) has been done to identify its constituent amino acids. Based on the rate of ammonia formation, a value for amide nitrogen of 1.9% was calculated by Ross (*7*). No attempt, however, was made by him to characterize this fraction further.

The work reported here was undertaken mainly to establish the presence or absence, and if present, the nature of the amides occurring in tobacco mosaic virus protein. At the same time the work of others, reporting amino acids to be components of the virus, was confirmed.

The analytical method of paper partition chromatography (*1*) was used and found to be particularly suitable for this work. Only a brief description of methods is given here. The technical aspects of the problem will be treated elsewhere in more detail.

The tobacco mosaic virus used in these experiments was prepared from leaves of greenhouse-grown Turkish tobacco plants which had been infected with the virus for 20 days. The method of purification consisted of 3 cycles of alternate low speed and high speed centrifugations. The final preparation had a bluish-white opalescence and electron micrographs showed inappreciable impurities.

The purified virus was subjected to enzymatic hydrolysis, since amides are known to be converted to their respective amino acids by the common methods of chemical hydrolysis. Pancreatin was added to heat-denatured virus protein, the pH was adjusted to 8.0, and the preparation was then incubated at 33° C. Appropriate controls of enzyme added to water were carried simultaneously. The course of hydrolysis was followed by withdrawing aliquots at intervals and testing them by paper chromatography. After the 10th day of incubation, no further changes were observed. The preparations were then heated to coagulate the enzyme and the resultant suspensions were cleared by filtration.

The acid—HCl—and alkaline—$Ba(OH)_2$—hydrolyses were carried out in an atmosphere of nitrogen in sealed

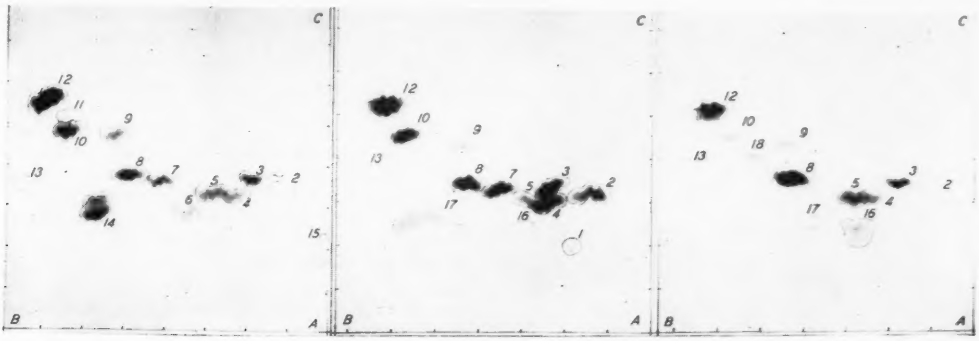

FIG. 1. Paper partition chromatograms of hydrolyzates of tobacco mosaic virus protein; left, pancreatic digest; middle, acid hydrolyzate; right, alkaline hydrolyzate. A–B, water-saturated phenol. A–C, *n*-Butanol-acetic acid-water. Spots: 1, cystine; 2, aspartic acid; 3, glutamic acid; 4, serine; 5, glycine; 6, asparagine; 7, threonine; 8, alanine; 9, tyrosine; 10, valine; 11, tryptophane; 12, leucine, isoleucine, and phenylalanine; 13, proline; 14, a peptide; 15, probably residual protein; 16, lysine; 17, arginine; 18, α-amino-*n*-butyric acid, believed to be an artifact probably originating from threonine.

glass tubes. These were autoclaved for 6 hr at 15 lb pressure. Excess HCl was eliminated by evaporation, and the $Ba(OH)_2$ by precipitation with H_2SO_4.

Each sample was chromatographed routinely in three solvent pairs. As the first solvent, water-saturated phenol was used invariably for all two-dimensional papers. For the run in the second direction, two solvents were employed, either 2–4 lutidine (1 vol) thoroughly shaken in water (1 vol), or freshly prepared *n*-butanol-acetic acid-water. Spots were revealed by spraying the dried sheets with 0.1% ninhydrin in 95% ethanol.

A chromatogram of the pancreatin digest is shown in Fig. 1 (left); the control gave only one faint spot in the position normally occupied by alanine. Asparagine, spot 6, was first tentatively identified by position and by its characteristic rusty color with ninhydrin. Positive identification was later achieved by demonstrating that the asparagine spot was intensified on both phenol/lutidine and phenol/butanol-acetic acid chromatograms by addition of authentic asparagine to the spot at the origin.

It was further shown that acid hydrolysis of the eluate from a cutout of the suspected asparagine spot resulted in its disappearance, with concomitant appearance of an aspartic acid spot. In Fig. 1 (left), the relatively weak spot due to aspartic acid (No. 2) compared to asparagine (No. 6) suggests that the virus protein contains more asparagine than aspartic acid. In the acid hydrolyzate (middle) the aspartic acid spot (No. 2) has been suggested by the conversion of asparagine to aspartic acid.

A spot in the position usually occupied by glutamine was found in chromatograms of aliquots taken during the early stages (before the 7th day) of incubation. Since confirmatory tests were not made, position alone may not be a sufficient criterion for identification; there remains the possibility that the spot may have been due to the presence of a peptide in the incomplete hydrolyzate. On the other hand, glutamine, being a labile compound, may have been destroyed during the prolonged incubation.

All of the amino acids previously reported to be constituents of tobacco mosaic virus protein have been identified by paper partition chromatography. In addition, the presence of one amide, asparagine, has been demonstrated and the probable occurrence of a second, glutamine, has been suggested.

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Effect of Hyaluronidase on the Subcutaneous Absorption of Electrolytes in Humans[1]

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Although observations have been made in animals on the effect of testicular hyaluronidase on the subcutaneous absorption of isotonic saline (*7*), diodrast (*9*), diphtheria antitoxin (*6*), and plasma proteins tagged with radioiodine (*2*), studies on humans have been limited to measurement of the speed at which large subcutaneous infusions can be given. Whereas direct observation of the behavior of intradermal wheals (*5, 8*) is possible in humans, exact data on subcutaneous injections are more difficult to obtain. Since hyaluronidase is currently being used to facilitate the subcutaneous administration of

[1] This investigation was aided by a grant from the Children's Research Foundation.

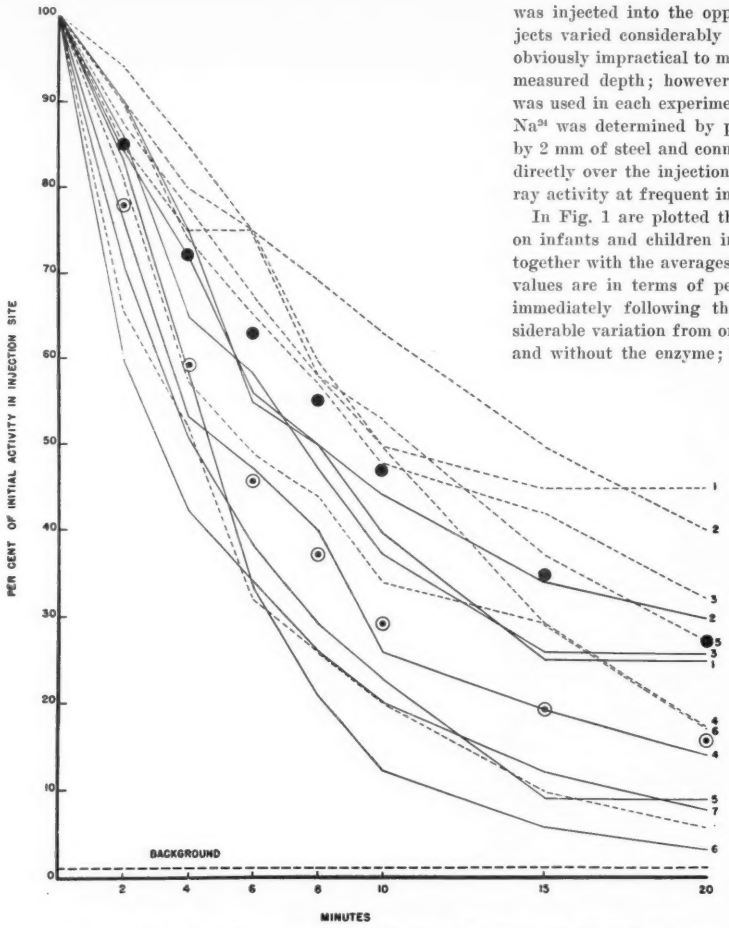

FIG. 1. Rate of disappearance of Na^{24} in isotonic saline from subcutaneous injection site, Control – – –, average ●: hyaluronidase ———, average ⊙. The numbers refer to individual subjects.

fluids to infants and children (*4*, *5*, *8*), it seemed advisable to quantitate its action on the absorption of electrolytes. The following experiments were carried out with 0.9% NaCl containing radiosodium (Na^{24}).[2] Observations were made on the rate of disappearance of Na^{24} from the injection site by means of an externally placed Geiger counter, and on the serum Na^{24} concentration following subcutaneous injection.

In the first group of experiments, 0.5 ml of saline solution containing 0.5–1.0 μc of Na^{24} was injected into the subcutaneous tissues of one forearm of the subject; a similar amount of Na^{24} to which had been added 25 turbidity reduction units of bovine testicular hyaluronidase[3] was injected into the opposite forearm. Since the subjects varied considerably in weight and physique, it was obviously impractical to make the injections at a constant measured depth; however, a similar injection technique was used in each experiment. The disappearance rate of Na^{24} was determined by placing a Geiger tube, shielded by 2 mm of steel and connected to a counting rate meter, directly over the injection site and recording the gamma ray activity at frequent intervals.

In Fig. 1 are plotted the results of seven experiments on infants and children in a normal state of hydration, together with the averages for all the subjects. Ordinate values are in terms of percent of the activity observed immediately following the injections. There was considerable variation from one subject to another both with and without the enzyme; however, in any given subject the addition of hyaluronidase definitely hastened the disappearance of Na^{24} from the injection site. The advisability of using each subject as his own control is apparent, for in some of the subjects the disappearance rate of Na^{24} was at least as great in the control injections as it was in others after addition of the enzyme. Furthermore, use of the enzyme produced different degrees of acceleration in the disappearance rate in different subjects.

In contrast to the definite effect noted in the normally hydrated subject, hyaluronidase did not appear to accelerate the subcutaneous absorption of Na^{24} in children with hypoproteinemic edema. In keeping with earlier studies on the disappearance of intradermal wheals (*1*), the few preliminary observations which we have made suggest that Na^{24} is absorbed somewhat more rapidly in the edematous subject as compared with the normal and that the disappearance curves of the control and enzyme injections are very similar.

In order to show that Na^{24} actually enters the blood from the subcutaneous tissues more rapidly under the influence of hyaluronidase, serum levels were followed in several normal subjects. In these experiments 2 μc of Na^{24} per kg body weight was injected into the thigh region by the method described by Barnett (*3*). The total volume of isotonic saline used was 4 ml. Serum samples were dried in metal dishes and assayed with a mica end window Geiger tube connected to a scaling circuit. In Fig. 2 are plotted the data from four subjects, each of whom received control and enzyme injections (150 units)

[2] Na^{24} was prepared in the Washington University cyclotron through the courtesy of A. A. Schulke and A. B. Phillips.

[3] Hyaluronidase ("Hyronase") was kindly supplied by the Schering Corporation, Bloomfield, New Jersey.

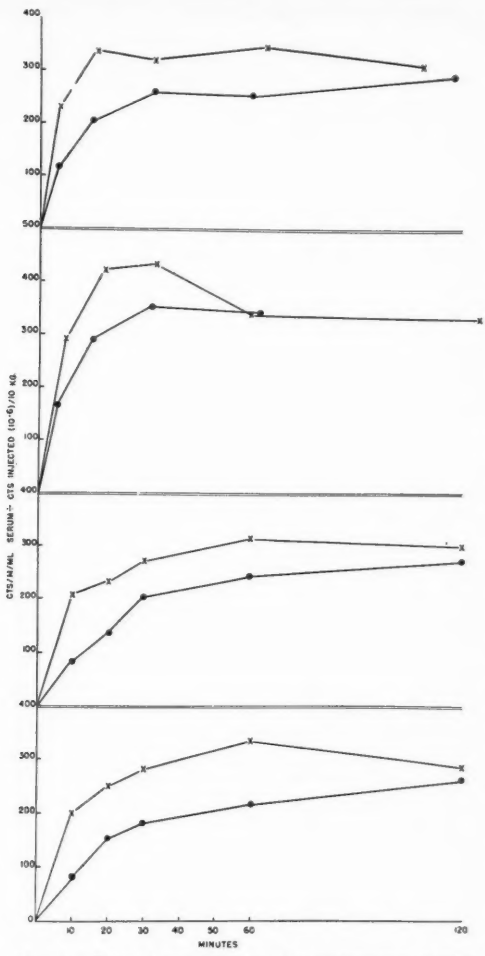

FIG. 2. Rate of serum uptake of subcutaneously injected Na^{24} in isotonic saline. Control ●——●, hyaluronidase ×——×.

on different days. Serum activity is expressed in terms of cpm/ml divided by counts injected (10^{-6}) per 10 kg body weight after correction for decay. Here, too, there was considerable variation in rate of absorption from one subject to another, despite correction of the data to constant body weight, but in each instance the serum Na^{24} value rose more rapidly when hyaluronidase was used.

From these observations, it is apparent that in the normally hydrated human subject, the rate of absorption of sodium ion from small volumes of subcutaneously injected fluid is enhanced by the addition of hyaluronidase.

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The Light Reaction in the Bleaching of Rhodopsin[1]

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The absorption of light by rhodopsin in the retina results in both the bleaching of the molecule and the excitation of rod vision. One could conclude at once that the bleaching of rhodopsin is the source of visual excitation, were it not a composite process. It consists of an initial photochemical change, followed by relatively slow thermal —i.e., "dark"—reactions. The light process converts rhodopsin to a highly unstable orange material (Lythgoe's "transient orange"), which breaks down in light or darkness to a yellow mixture of retinene$_1$ and protein (Lythgoe's "indicator yellow") (*6, 8*). In the retina these substances are involved in further changes, but in ordinary solutions of rhodopsin this is all that occurs.

The first product formed by the action of light on rhodopsin is removed so rapidly that early attempts to measure its spectrum led only to approximations (*7, 8*). In 1941, however, Broda and Goodeve reported an experiment that appeared to isolate the light reaction (*2*).

These workers prepared solutions of rhodopsin in mixtures of glycerol and water (3:1) such as Kühne had examined more than 60 years before (*3*). On cooling to −73° C such solutions vitrify. The absorption band of rhodopsin was reported to shift about 10 mμ toward the red and to become much narrower in shape. On exposure to light at −73° C, the absorption maximum moved about 5 mμ toward the blue, and fell some 12 % in height. This was the light reaction. The photoproduct remained stable at the low temperature. It did not appear to vary in spectrum between pH 6 and 9, confirming an earlier conclusion of Lythgoe and Quilliam concerning transient orange. On warming to room temperature in the dark it decomposed spontaneously to indicator yellow.

We have reexamined this behavior of rhodopsin at low temperatures. Spectra were measured with the Beckman spectrophotometer in a specially designed Dewar flask, silvered except for a window. The rhodopsin solution, well buffered in a glycerol-water mixture (2:1) was suspended inside the vessel in a quartz cell over liquid air or solid carbon dioxide. The temperature of the solu-

[1] Supported in part by a grant from the Medical Sciences Division of the ONR. Low temperature experiments performed by Mr. St. George, those on rhodopsin films by Mr. Durell. Preliminary tests on rhodopsin films were also made by Lionel Jaffe.

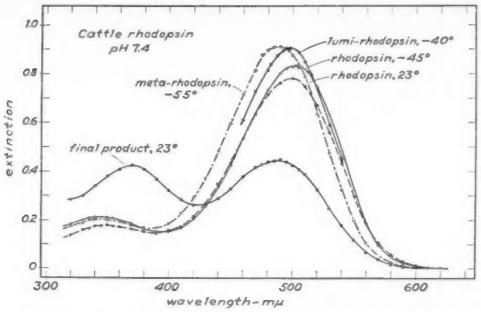

FIG. 1. Bleaching of rhodopsin at low temperatures in a glycerol-water mixture (2:1). The spectrum was measured at 23° C and again at −45° C. The solution was then exposed to intense white light at the low temperature until all changes were completed (lumi-rhodopsin). It was then warmed to −15° C in darkness, left at this temperature until all changes were completed, and recooled to −55° C prior to remeasurement (meta-rhodopsin). Finally the solution was warmed to room temperature in darkness, and the spectrum of the final product was measured. This was a mixture of regenerated rhodopsin and of retinene$_1$ (max 375 mμ) + protein in roughly equal amounts. All these spectra have been corrected for changes in volume of the solvent with the changing temperatures.

tion was measured with a thermocouple immersed in it. Parallel experiments with cattle and bullfrog preparations yielded similar results, with one small difference as noted below.

A series of measurements made with cattle rhodopsin in neutral solution is shown in Fig. 1. The maximum absorption in the glycerol-water mixture at room temperature lies at about 500 mμ. On cooling to −30°–−100° C, the maximum shifts progressively 5–9 mμ toward the red, and rises 6%–14% higher than would be caused by contraction of the solvent; but the shape of the band changes very little. On exposing the solution to light at these low temperatures, the maximum shifts about 5 mμ toward the blue, rising about 5% in height in cattle rhodopsin, falling about this amount in frog rhodopsin, still with little change in shape. This is the light reaction. We shall call its product *lumi-rhodopsin.*

If the solution of lumi-rhodopsin is warmed to about −20° C, a further change occurs in darkness. The absorption band shifts another 7–9 mμ toward the blue, with little further change in height or shape. (The solution shown in Fig. 1 had been warmed to −15° C until all changes were completed, then recooled to −55° C for measurement.) We shall call this second product *meta-rhodopsin.* Neither its spectrum nor that of lumi-rhodopsin changes consistently with pH, between pH 3.9 and 10.1, nor is either substance affected appreciably by further exposure to light. Note that the change from lumi- to meta-rhodopsin at −20° C is unmistakably a distinct process. Not only is no retinene$_1$ formed during this conversion, but absorption in the region of the retinene$_1$ maximum (about 375 mμ) tends to fall a little.

On allowing the solution of meta-rhodopsin to rise to room temperature in darkness, it goes over to a mixture of regenerated rhodopsin and retinene$_1$ + protein in roughly equal amounts. On a second exposure to light at room temperature, the regenerated rhodopsin bleaches to a final mixture of retinene$_1$ and protein alone.

The changes in color associated with the light reaction and with the further change to meta-rhodopsin are very small—from red to orange-red, with little change in depth. By merely looking at these solutions before and after exposure to light, one could not have been certain that any change had occurred at all.

Many years ago, Kühne observed that when retinas have been thoroughly dried over sulfuric acid, their rhodopsin scarcely seems affected by even an hour's exposure to direct sunlight (*5*). It occurred to us that here, as in the cold, the light reaction might be completed, but with so little change in color as to escape notice.

To examine this possibility we prepared dry gelatine films of rhodopsin of a quality suitable for accurate spectrophotometric examination. Weigert and his coworkers had prepared similar films in their studies of photodichroism (*10*). Solutions of frog or cattle rhodopsin in 4% digitonin were mixed with one-third their volume of warm 10% gelatine, and were poured on heavy celluloid film. After setting, the film was dried in a desiccator over calcium sulfate ("drierite") for at least 3–4 days. By this time the rhodopsin film had curled off or could be peeled off the celluloid. All these operations were carried out in darkness or under dim red light. As blanks, similar films were prepared in which digitonin solution alone was substituted for the rhodopsin.

Measurements made with a dry gelatine film of cattle rhodopsin are shown in Fig. 2. Bullfrog preparations exhibit almost identical behavior. The absorption spectrum of rhodopsin in the film is remarkably similar to its spectrum in aqueous solution. The maximum lies at 495–498 mμ. On exposure to a short, intense burst of light—in Fig. 2 the approximately 0.02-sec flash of a photoflash lamp—the maximum shifts about 6 mμ toward the blue, and rises about 10% in height. This is lumi-rhodopsin. Within the next 15 min at room temperature in light or darkness the spectrum shifts a further 5–10 mμ toward the blue, simultaneously falling slightly in height. This is the conversion of lumi- to meta-rhodopsin. The meta-rhodopsin remains stable for days in the dry state, and is not affected by further exposure to light. On wetting the film with water, however, meta-rhodopsin goes over in the dark to a mixture of regenerated rhodopsin and retinene$_1$ + protein in roughly equal amounts. Prior to measuring the spectrum of this product, the film is redried. On reexposing the dried film to light, the regenerated rhodopsin goes through the same changes as did the original pigment.

Thus in the dry state, as in the cold, rhodopsin goes through the light reaction unhindered, and the dry photoproduct also is converted slowly to meta-rhodopsin; but neither regeneration nor formation of retinene$_1$ can occur.

The bleaching of rhodopsin therefore involves the following stages: Light converts rhodopsin to lumi-rhodopsin. At temperatures in the neighborhood of −20° C, or at room temperature even in the dry state, lumi-rhodopsin goes to meta-rhodopsin. The nature of these changes

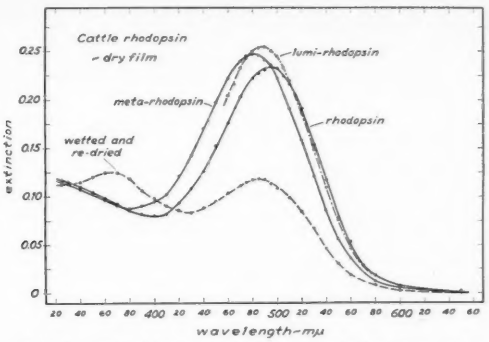

FIG. 2. Bleaching of rhodopsin in gelatine film. The spectrum of rhodopsin was measured in a film dried over calcium sulfate. It was then exposed to the instantaneous illumination of a photoflash lamp, and the spectrum recorded within the first minute thereafter (lumi-rhodopsin). After about 1 hr in darkness at room temperature the spectrum was remeasured (meta-rhodopsin). These changes were complete; a second exposure to a photoflash lamp produced no further effect. The film was then soaked in *m*/15 phosphate buffer, pH 7.2, for 10 min and redried, all in darkness. The spectrum of the final product shows a mixture of regenerated rhodopsin and of retinene$_1$ + protein in roughly equal amounts.

is still obscure; one thinks of ionization or the formation of a free radical, followed by molecular rearrangement, but this must await further study. Given access to water and a high enough temperature to permit thermal activation, meta-rhodopsin is transformed on the one hand to rhodopsin, on the other to retinene$_1$ and protein.

This is not a wholly exhaustive description of the bleaching process under all conditions, but it probably goes as far with the early stages of bleaching as will be found useful. Our observations in extreme cold indicate complexities in the light reaction itself, not unexpected in so complex a molecule as rhodopsin. The primary reason for stopping with the stages we have named is their stability under specific conditions of bleaching. The relatively stable end product of bleaching rhodopsin at temperatures below – 40° C is lumi-rhodopsin. The relatively stable product of bleaching rhodopsin at about – 20° C or in the dry state is meta-rhodopsin. The stable products of bleaching ordinary solutions of rhodopsin at room temperature are retinene$_1$ and protein, or a mixture of these substances with regenerated rhodopsin if the solutions are replaced in darkness following irradiation.

Further complexities can also be found in the later stages of bleaching. In acid solutions (pH about 4) meta-rhodopsin yields an orange intermediate with maximal absorption at about 440 mμ, which is transformed only in the course of several hours at room temperature to retinene$_1$ (*8*). Also retinene$_1$ has the capacity to couple spontaneously with a wide variety of amino compounds (*1*). It is formed in association with rhodopsin-protein, and undoubtedly remains coupled in part with this molecule; but in part it also leaves this protein to go into the free state and to couple with other retinal molecules. One such reaction which has already been demonstrated in more complete systems than those just described is the migration of retinene$_1$ from rhodopsin-protein to the apoenzyme, retinene reductase, prior to its reduction to vitamin A$_1$ (*9*).

The light reaction, however, seems to possess much the same characteristics under all the circumstances we have explored. It proceeds at roughly the same rate at very low temperatures and in the dry state as in aqueous solutions in the warm. Accurate measurements made with dry films show it to be a first-order process, proportional in rate to the light intensity. These are the conventional properties of a simple photochemical process, the rate of which depends only upon the rate of absorption of quanta of light. When Hecht, years ago, found these properties in the over-all bleaching of rhodopsin in solution (*4*), it was because his experiments were performed in such a way that the light reaction was the limiting process.

The observations we have described reveal a striking parallel between the bleaching of rhodopsin and the photographic process. In both cases light produces a scarcely visible change—a "latent image"—followed by gross thermal changes. The parallel is particularly close in the dry rhodopsin film, in which light produces a stable latent image composed of meta-rhodopsin, which can be "developed" at any later time simply by wetting. Here, development induces bleaching, and results in a positive.

These observations also reflect upon the relation between the bleaching of rhodopsin and the excitation of rod vision. We are still as far from knowing the mechanism of excitation in the retinal receptors as in muscle or nerve. Nevertheless, something of the relation between visual stimulation and bleaching can be inferred from the times involved in both processes. When an eye is exposed to light, an electrical discharge can be recorded from the optic nerve within periods of the order of tenths of a second, even in cold-blooded animals. The excitation of the rods themselves must occur much earlier than this. It seems probable that the formation of retinene$_1$ is too slow a process to account for this response. More likely it depends upon the light reaction itself, or upon some further change—such as the conversion of lumi- to meta-rhodopsin—so intimately associated with the light reaction as to follow it to completion within a small fraction of a second.

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Comments and Communications

Language in Science

[This communication is reprinted from the "Letters to the Editor" section of *The Lancet*, June 11, 1949, by permission of that publication and of the author.]

Until a very recent stage of man's history the search for knowledge was in the hands of a priesthood who guarded most carefully their privileged position. Often the power of this priesthood lay in the ignorance and superstition of those without the order. By the use of language unknown to most people they prevented knowledge from passing to the outsider.

After the Renaissance, English came to be used as the language of science and religion in this country, and knowledge was put within the reach of many more people. But today the growing complexities of science are causing a change in the reverse direction. In medicine, for example, each branch is building up a special and ever increasing vocabulary, and this is producing a new series of priesthoods—the hematologists, the venereologists, the stereochemists, the biophysicists, the cytologists, the pure and applied mathematicians, the epidemiologists. The subdivisions of knowledge will lose much of their value unless the results of applying their special techniques are intelligible to others besides the various high priests.

Of late years books have been written to try to pass on the secrets of the new priesthoods, and these "popular" books show one way in which the problem has been tackled. Another possible solution appeared in the services during the late war. This was a slang which covered both everyday and technical subjects; it was a live method which filled a gap. These examples illustrate two principles which could be used to prevent even greater chaos than at present: either language can be simplified or a new language can be evolved.

Ogden with Basic English has shown how speech can be simplified, and Hogben has suggested an international language of science with his *Interglossa*. Yet another, Bodmer, in *The Loom of Language* (p. 48) has emphasised the keynote: "The invention of the alphabet made it possible to democratize reading as the invention of the number 0 made it possible to democratize the art of calculation." An alphabet or a Basic English for science and medicine is a pressing need.

The realisation of this aim is not easy, but every editor of a journal can help by insisting on papers being written in the simplest possible language, and frowning upon new words which could easily be rendered in simple terms; every author can help by writing in simple language. It is asking too much to expect that specialised techniques can be so described that their features are at once understood by a worker in an unrelated field, but it is not asking too much to insist that the main lines of argument in a paper should be presented with consideration for the difficulty of a worker in another field.

Unless steps such as these are taken now by editors and edited, scientific and medical workers will soon be struggling in a bog of words. This is a system of planning which requires no committee, and the benefit to knowledge would be incalculable. The pedant has always been a butt for the wit. Now is the time to banish him firmly from the various branches of knowledge.

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Anthropologists vs. the Atom Bomb

In his recently published *The Science of Culture* (p. xii), Prof. Leslie A. White refers to certain comments by E. U. Condon published in these columns (*Science*, 1946, **103**, 415) and also to a letter of mine in this journal (*Science*, 1946, **103**, 570) in which I told of a resolution proposed by myself and seconded by Margaret Mead, and adopted by the American Anthropological Association in December 1945, pledging anthropologists to work with other scientists to make "appropriate social inventions" to "guard against the dangers . . . inherent in atomic use." Prof. White comments on this, "No report on progress toward such inventions has appeared yet."

This is not quite correct. Early in 1946 I commenced to make use of several social inventions directed toward achieving the end set out in the resolution. By October 1946 this resulted in an animated sound film which has been distributed under the title "One World Or None." I understand that this film has been seen by hundreds of thousands of persons and in every state of the union. It has been described by a well-known bureau of propaganda analysis as "the most effective documentary ever made," and the film may be obtained from the National Committee on Atomic Information, Washington, D. C.

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Correction

We wish to correct an obvious error in our paper, "The Crystalline Form of Sodium Ascorbate" (Science 1948, **108**, 713).

On page 713 the sentence at the top of the second column should read:

Forty grams (1 mole) of ascorbic acid was dissolved in 600 cc of hot absolute methyl alcohol. While still hot, it was treated under stirring with 250 cc of a warm solution of methyl alcohol containing 12.3 g (1 mole) of sodium methylate.

The structure of sodium ascorbate as given by the U.S.P. (XIII, p. 898) was shown in our paper with the sodium substituting the acidic hydrogen of the carboxyl

group, but we stated that it is commonly believed that the neutralization involves the hydroxyl group attached to the third carbon. We should also have added that with neutralization of this enolic hydroxyl group by sodium, the lactone ring of the ascorbic acid remains unbroken unless excess of sodium is added. The values found for carbon, hydrogen and sodium in the analysis of our sodium ascorbate are in agreement with the theoretical values calculated for the sodium lactone salt.

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In Defense of the USDA Research Administration

Although parts of the curious paper by W. Gordon Whaley, "The Agricultural Impasse" (*Science*, July 22) are obscure, others suggest serious deficiencies in the Research Administration of the Department of Agriculture. If believed, these statements might reduce the effectiveness of this administration's work.

Certainly the research bureaus of the department, including the Bureau of Plant Industry, Soils, and Agricultural Engineering, which Mr. Whaley finds especially deficient, have many administrative problems—in fact, most of those he mentions. But the inference that these problems go unrecognized is not so. Fundamental as well as applied research is encouraged. Many projects are suggested by junior scientists. Ranks and salaries of strictly research scientists can be (and some are) as high as those of division chiefs and assistant chiefs of bureau.

Scientists need the freedom essential for effective research, but they are not an elite class—Congress must have ultimate control of public funds. The reports of annual hearings have their bad spots; they also have many good ones. The problem is to improve the relationship, not to avoid it.

The administrative and personnel problems of the Agricultural Research Administration that Mr. Whaley touches on are far more complex than he has had an opportunity to appreciate (else he would not call the task "dignified pussyfooting"). As in any other research group, the problems keep coming. The question is, how are they handled? Mr. Whaley thinks they are handled very badly; I think they are handled well.

Possibly Mr. Whaley conceives of research in terms of many small independent projects. There are some of these. But agricultural scientists must address themselves increasingly to problems of great scope. A large part of our big research undertakings are cooperative with many other agencies, especially the Land Grant Colleges, and are managed almost wholly by the research scientists themselves. The prestige of the plant scientists, about which Mr. Whaley says he is worried, is not only high, and increasing, for their professional work, but also for their cooperative methods of administration. How well are they doing? Look at the record!

In the same paper Mr. Whaley quickly writes off the tropics. He even asserts that these regions cannot become important producers of "energy" crops. Should they hear of it, successful sugar cane planters and other farmers in Hawaii, northern Queensland, and wherever modern methods are used in the humid tropics would be puzzled. The problems of tropical agriculture are indeed complex, but the worst error of all would be to neglect them, if we want abundant food in the world.

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An Automatic Timer for Speakers

Timing devices available for notifying speakers that their allotted time has elapsed are generally cumbersome and require outside power sources. Many of these appliances in present use require alternating current, which is not easily obtained in hotels and meeting halls which produce their own direct current. Further, the mechanisms now in use mark the time allotted but do not remind the speaker that his time has run out.

We have recently designed a simple, compact, portable timing device which requires no outside source of electrical current. A commercially available timer is modified by the introduction of contacts for the completion of a circuit between three small flashlight batteries and a six-volt buzzer. An escapement type lever arm is introduced into the timing device to make it possible to turn on a light and to sound a buzzer for brief periods. The entire unit weighs less than one pound.

The chairman sets the time allotted on the timer. The time remaining to the speaker is indicated on the face of the dial. The warning light turns on automatically two minutes before the end of the specified period. At the end of the allotted period a buzzer sounds momentarily. One and a half minutes after the supposed end of the talk, the buzzer sounds again, this time for a longer period. Three minutes following the scheduled end of the talk, the buzzer sounds continuously for one minute to remind the speaker that he has overstayed his invitation. Varying times for these signals may be installed. The automatic character of the signal relieves the chairman of the occasionally unpleasant task of bringing the presentation to a close. This device has been tested satisfactorily at several meetings.

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Book Reviews

Subsurface Geologic Methods: A Symposium. L. W. LeRoy and Harry M. Crain. (Eds.) Golden, Colo.: Dept. of Publ., Colorado School of Mines, 1949. Pp. 826. (Illustrated.) $6.00, paper; $7.00 cloth.

The search into the unknown has always intrigued both young and old. Tales of the jungle explorer or of the one to brave the cold polar wastes, have fascinated man since first these stories were told. This search, while necessary to balance the economics of industry, also lends some thrill to the otherwise drab existence of the scientist. Surely everyone knows how easy it is to pump a few gallons of gasoline into the tank of his automobile, by merely pushing a switch; but, only the scientist realizes the tireless search, the days of planning, and the excitement of discovering the petroleum reservoir that will later yield the refined product that will be pumped into his car.

The methods of the search into the unknown beneath the surface of the earth are the subjects discussed in this book. The editors have succeeded in placing before the reader a clearly written volume on the geologist's technique. It is concise, free of too much trade jargon, profusely illustrated with apt diagrams and sharp photographs, and quite comprehensive. That the majority of the 826 pages deal with the geologist's search for petroleum is understandable when we consider that this field of commerce has penetrated deeper, and in regions more widely, than any other field of industry. Cost of drilling and producing has increased so greatly that careful planning is a necessity before the earth is punctured. For years the petroleum industry has set aside large sums for research connected with discovering new reserves. This research is the subject of the present volume.

In the beginning, consideration is given to the type of structure required for satisfactory production, and this is accomplished by correlating various observations to reconstruct sections, coordinate sequences, to interpret earth history, etc. Once the structure is known, the driller has at least a negative norm to guide him.

Laboratory inspections of samples are explained; these include micropaleontology, petrofabrics, and sand grain characteristics, among other tests. Well logging is important, and the explanations include logging of the strata, electrical resistance logging to measure oil content, and logging the muds and cuttings. An explanation of the geophysical methods employed is brief but sufficiently comprehensive for the geologist. Here he will learn how important these tools are to his own work. Seismic, gravitational, electrical, and magnetic methods are dealt with, and some case histories given. Finally, a few applications of subsurface geology and geophysics to other civil engineering problems are briefly explained.

In a sense, the title of this book might be misleading to some. The engineer who is located in the eastern United States and who is interested in highway location and design, or shallow bridge foundations, building foundations, or ground water supplies for municipal use, will find little in this book to help him. Some mining engineers might feel their field is not sufficiently covered from the geologic standpoint. However, those interested in any phase of the petroleum industry will find this book most helpful, and it is a required volume for the shelves of any geology library.

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Les Lipides. (Colloques Internationaux du Centre National de la Recherche Scientifique, Paris, 5 au 12 Janvier 1948, Vol. XI). Paris Ve: Service des publications du C. N. R. S., 1949. Pp. 399. 1000 fr.

This new book contains 26 papers (19 in French and 7 in English) delivered by 24 different scientists (18 French, 1 English, 1 Dutch, 2 Swiss, and 2 Americans) at a symposium on lipids that took place in Paris, January 5–12, 1948. The papers had already been published, constituting Nos. 1, 2, 3 and 4 of volume II of *Archives des Sciences Physiologiques.*

The book is divided into eight parts: digestion and intestinal absorption of lipids, deposition and mobilization of depot fats, transport of lipids in the blood, lipoproteins, metabolism of higher fatty acids, desaturation of higher fatty acids and the essential fatty acids, lipids and blood clotting, phosphoaminolipids and products of their degradation, and oxidation *in vitro* of fats and antioxidants.

Papers presented are of uneven merit, some being excellent and some being obviously the product of a hurried effort. The part on lipoproteins is the best. It includes an excellent review paper by Macheboeuf, which presents a comprehensive picture of that writer's work, from his earliest pioneer experiments up to 1947. An article by Chargaff follows, with an authoritative discussion of cellular lipoproteins. Finally, Frazer discusses his interesting work on artificial lipoproteins. Among other papers, a review on ketone bodies by Barnes and Gurin is outstanding.

As a symposium on lipids, the value of the book is limited. Most of the material it contains is either widely known or has been covered more comprehensively by earlier reviews. Unfortunately, many of the participants are not abreast of developments in recent English and American scientific literature, presumably because of circumstances beyond their control. Two lines of work on lipids which have been especially active in the last decade —namely, lipotropic factors and chemical structure of complex lipids—are not discussed. Indeed, the absence of these two topics, makes the reader feel that the book belongs to a much earlier date than 1949.

The book is most interesting as a cross section of French work and French ideas in the field of lipids. It

is encouraging to see that, in spite of many difficulties, French science has traveled a long way on the road to full recovery.

JORDI FOLCH-PI

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Experimental Psychology: An Introduction. Leo Postman and James P. Egan. New York: Harper, 1949. Pp. xiv + 520. (Illustrated.) $4.50.

Instructors who have tried Woodworth's *Experimental Psychology* for undergraduate courses and found the going tough will welcome this new book by Postman and Egan. It covers much the same subject matter areas as Woodworth but is more selective within these areas, briefer, and delivered at a level well within the undergraduate grasp.

Chapters are distributed as follows: psychophysical methods, 1 chapter; the senses and perception, 8; judgment, 1; reaction time and association, 1; learning and memory, 6; emotional behavior and social behavior, 1 each. In general, the discussion treats method and experimental results. The elaboration of theory is almost, but not entirely, lacking. At the close of each chapter is the outline of one or more laboratory experiments which illustrate and apply the methods and techniques discussed.

Readers will find the book organized so as to make it very teachable. Good use has been made of outlining legends and paragraph headings, illustrations appear in considerable number, and chapter bibliographies are broken down by research topic. Problems associated with the control of stimulus or subject variables are given particular attention in sections at the close of many of the chapters. Certain methodological sections should also be helpful—for example, the one which integrates the concepts of reaction time, judgment time, and latency, and another which describes the traditional psychophysical methods as models and models only, which individual experiments may follow to greater or less degree.

As the authors themselves point out in their introduction, the book does not treat all the areas or problems now embraced in experimental psychology, but proposes to offer a representative sample of the methods and results in experimental psychology. Perhaps the only serious question which potential users of the book may face is the question of whether the topics thus selected overlap too seriously those discussions of the senses, perception, and learning which the student may have read in a general text used in some prior introductory course.

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Scientific Book Register

CHAUCHARD, PAUL. *Le Système Nerveux Sympathique: La régulation nerveuse de l'activité viscérale.* Paris (VII^e): Librairie Gallimard, 1949. Pp. 364. (Illustrated.) 490 fr.

COPENHAVER, JOHN W., and BIGELOW, MAURICE H. *Acetylene and carbon monoxide chemistry.* New York: Reinhold Publ., 1949. Pp. xvi + 357. (Illustrated.) $10.00.

CROW, LEONARD R. *Learning electricity and electronics experimentally.* Vincennes, Ind.: Scientific Book Publ., 1949. Pp. xi + 525. (Illustrated.) $4.40 postpaid.

CROW, LEONARD R. *Saturating core devices: Operating principles and applications.* Vincennes, Ind.: Scientific Book Publ., 1949. Pp. xiv + 373. (Illustrated.) $4.20 postpaid.

CUSTER, R. PHILIP. *An atlas of the blood and bone marrow.* Philadelphia-London: W. B. Saunders, 1949. Pp. x + 321. (Illustrated.) $15.00.

DARLINGTON, C. D., and MATHER, K. *The elements of genetics.* New York: Macmillan, 1949. Pp. 446. (Illustrated.) $3.75.

DIXON, MALCOLM. *Multi-enzyme systems.* New York (10): Cambridge Univ. Press, 1949. Pp. 100. (Illustrated.) $1.75.

EDDY, WALTER H. *Vitaminology: The chemistry and function of the vitamins.* Baltimore: Williams & Wilkins, 1949. Pp. v + 365. (Illustrated.) $6.00.

ELMORE, WILLIAM C., and SANDS, MATTHEW. *Electronics: Experimental techniques.* New York: McGraw-Hill, 1949. Pp. xviii + 417. (Illustrated.) $3.75.

FINCH, VERNOR C., and TREWARTHA, GLENN T. *Elements of geography: Physical and cultural.* (3rd ed.) New York-London: McGraw-Hill, 1949. Pp. x + 711. (Illustrated.) $6.00.

FOSTER, JACKSON W. *Chemical activities of fungi.* New York: Academic Press, 1949. Pp. xviii + 648. (Illustrated.) $9.50.

FREEMAN, OTIS W., and RAUP, H. F. *Essentials of geography.* New York-London: McGraw-Hill, 1949. Pp. vii + 487. (Illustrated.) $5.00.

FRIEDBERG, CHARLES K. *Diseases of the heart.* Philadelphia-London: W. B. Saunders, 1949. Pp. xxxii + 1081. (Illustrated.) $11.50.

HEISENBERG, WERNER. *The physical principles of the quantum theory.* (English translation by Carl Eckart and Frank C. Hoyt.) New York: Dover Publs., 1949. Pp. xii + 184. (Illustrated.) $2.50.

HOGBEN, LANCELOT. *From cave painting to comic strip: A kaleidoscope of human communication.* New York (22): Chanticleer Press, 1949. Pp. 287. (Illustrated.) $5.00.

HOUWINK, R. *Fundamentals of synthetic polymer technology: In its chemical and physical aspects.* (2nd ed.) New York: Elsevier Publ., 1949. Pp. xii + 258. (Illustrated.) $4.75.

HUTT, F. B. *Genetics of the fowl.* New York: McGraw-Hill, 1949. Pp. xi + 590. (Illustrated.) $6.50.

HUXLEY, JULIAN. *Heredity East and West: Lysenko and world science.* New York (21): Henry Schuman, 1949. Pp. x + 246. $3.00.

JACOBS, MORRIS B. *The analytical chemistry of industrial poisons, hazards, and solvents.* (2nd ed.) (Chemical Analysis, Vol. I.) New York-London: Interscience, 1949. Pp. xviii + 788. (Illustrated.) $12.00.

JAMES, GLENN, and JAMES, ROBERT C. (Eds.) *Mathematics dictionary.* (Rev. ed.) New York: D. Van Nostrand, 1949. Pp. v + 432. (Illustrated.) $7.50.

PENROSE, LIONEL S. *The biology of mental defect.* New York: Grune & Stratton, 1949. Pp. xiv + 285. (Illustrated.) $4.75.

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(Continued from page 171.)

detection of the S_f 10–20 molecules when present in low concentration depends upon the concentration effected in our preliminary ultracentrifugal purification and upon the sensitivity of the optical method of detection subsequently used. We can readily detect 5 mg% of S_f 10–20 molecules by our methods (representing approximately 1 mg% of cholesterol in this fraction). Thus a significant concentration of molecules of the S_f 10–20 class may be present in serum and still represent numerically, but not physiologically, an insignificant fraction of the total serum cholesterol. These facts help explain why it has not been possible for previous workers to reach any definite conclusions concerning atherosclerosis by studying analytical cholesterol values.

The patients with hypercholesteremia (over 300 mg%), drawn from the individuals without known disease, from the diabetics, and from the patients with myocardial infarctions, show no essential differences ultracentrifugally in the nature of the molecules transporting cholesterol, but instead show generally an increase in the quantity of cholesterol of serum bound in the form of the S_f 10–20 class of molecules. However, many normocholesteremic individuals may carry much more cholesterol in this fraction (S_f 10–20 molecules) than do the hypercholesteremics. Thus since normocholesteremic individuals and hypercholesteremic individuals may have appreciable concentrations of S_f 10–20 molecules, it is understandable that individuals of both these groups should develop atherosclerosis, assuming our thesis of the relation of S_f 10–20 molecules to atherosclerosis to be correct. This would provide, then, a missing link between these groups that had not been available from the study of analytical cholesterol levels.

In summary, the mechanism of cholesterol transport in the serum of rabbits and humans via giant lipid and lipoprotein molecules of low density has been characterized. In both species there exist classes of molecules of higher S_f rate and lower density than the major group of cholesterol-bearing lipoproteins. The evidence indicates that the lower density of the molecules of higher S_f values is at least partly due to a lower content of protein per molecule.

Evidence implicating the cholesterol-bearing molecules of the S_f 10–30 class in the production of cholesterol-induced atherosclerosis in the rabbit has been presented.

A study of 104 patients with proved myocardial infarctions reveals an almost universal occurrence of cholesterol-bearing molecules of the S_f 10–20 class (a class of molecules similar in many respects to the S_f 10–30 class in rabbits) at fairly high levels in the blood. All categories of normal humans studied show a lower frequency of occurrence of measurable concentrations of S_f 10–20 molecules than do the myocardial infarction patients (a group of patients almost all of whom have coronary artery atherosclerosis). The findings in the groups other than the myocardial infarction group are also consistent with the expected incidence of atherosclerosis in such groups.

Preliminary evidence indicates that exogenous cholesterol in the human as well as in the rabbit is a factor in influencing the blood level of molecules of the S_f 10–20 class.

Studies are now in progress with other categories of patients who develop atherosclerosis to a degree beyond that for supposed normal individuals of corresponding ages. These categories include hypertensive patients, patients with the anginal syndrome but without proved infarctions, nephrotic patients, and hypothyroid patients. In addition, long term studies of the effect of diet, with and without adjunctive drugs such as thyroid, lipotrophic factors, and possibly sex hormones, on the blood level of molecules of the S_f 10–20 class are continuing. All these groups should help to evaluate further the role of these giant molecules in the development of atherosclerosis.

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NEWS and Notes

Joseph C. Boyce has been appointed associate director of the Argonne National Laboratory. Dr. Boyce, at present professor of physics and chairman of the Department of Physics in the College of Engineering of New York University, will assume his new duties in July.

Paul B. Pearson, who has been acting chief of the Biology Branch, Division of Biology and Medicine, U. S. Atomic Energy Commission since last September, has been appointed chief of the branch. Dr. Pearson will supervise the biology research program of the AEC, which includes work in the fields of biochemistry, genetics, and physiology at AEC installations and AEC-supported research projects at colleges and universities.

Maurice B. Visscher has taken over the chairmanship of the National Research Council Committee on Unesco, replacing **Bart J. Bok,** who leaves for South Africa on February 17 (see *Science*, January 27, p. 101). Communications formerly addressed to Dr. Bok should now be sent to Dr. Visscher, Department of Physiology, Medical School, University of Minnesota, Minneapolis 14.

Howard J. Curtis, professor of physiology at Vanderbilt University School of Medicine, will give a series of special seminars at the University of Texas Medical Branch, Galveston, March 25–26. His subjects will be "Conduction in Nerve and Muscle" and "The Biological Effects of Nuclear Radiations."

Clark E. Thorp has been named chairman of chemistry and chemical engineering research at Armour Research Foundation of Illinois Institute of Technology. Dr. Thorp, who is an authority on ozone technology, will head a department of 95 scientists and technicians now engaged in research projects for industrial concerns and government agencies. He has been with the foundation since 1941.

Isay Balinkin, associate professor of experimental physics at the University of Cincinnati, has been elected chairman of the Inter-Society Color Council. The council serves as a liaison group for scientific, professional, and industrial organizations dealing with color.

Leo Otis Colbert, director of the U. S. Coast and Geodetic Survey, has been appointed to the Marine Laboratory Advisory Committee of the University of Miami.

Edward Rosenberg, chief of the Arthritis Clinic at Michael Reese Hospital, has been appointed assistant professor of medicine at the Chicago Medical School. Dr. Rosenberg is known for his work in arthritis, particularly with ACTH and cortisone.

Visitors to U. S.

Lancelot Hogben, professor of medical statistics, University of Birmingham, England; **Marcel Nicolet,** director of the Department of Radiation, Royal Meteorological Institute, Ucele, Belgium; **H. L. Ranson,** Advance Components, Ltd., London, England; **D. A. Temple,** chemist, Cambridge University, Cambridge, England, and **Han San Ryu,** engineer, Department of Commerce and Industry, Seoul Korea, were recent visitors at the National Bureau of Standards.

A. H. McIntosh, of the Rothamsted Agricultural Experiment Station, Harpenden, England, has joined the Entomology Department of the Connecticut Agricultural Experiment Station for a year, under an exchange agreement between the two stations.

G. Pauletta, director of research for the Carlo Erba Company of Milan, Italy, arrived at the University of South Dakota on February 2 to consult with Donald Slaughter, dean of the Medical School, and Jacob Belagorsky, assistant professor of pharmacology, on experimental work the school is doing on one of the Carlo Erba Company's preparations.

Georges Henri Rivière, associate general director of the International Council of Museums, visited the principal museums here last month, after spending seven weeks in Haiti, where he assisted the government in setting up a projected folk museum in Port-au-Prince. M. Rivière is curator of the new Museum of French Ethnology and Folk Art in Paris, to be opened soon.

Charles C. Macklin, Department of Histological Research, Faculty of Medicine, University of Western Ontario, Canada, will deliver the 26th Lewis Linn McArthur Lecture of the Frank Billings Foundation, Institute of Medicine of Chicago, at the Palmer House, Chicago, on February 24. His subject will be "The Alveoli of the Mammalian Lung: An Anatomical Study with Clinical Correlations."

Grants and Awards

A three-year grant of $50,000 per year from the Rockefeller Foundation has been made to the **Roscoe B. Jackson Memorial Laboratory,** Bar Harbor, Maine. Effective March 1, the grant continues the support the foundation has given for the past five years toward the laboratory's behavior studies. Dr. John P. Scott is administrator of the Behavior Laboratories. Working with him are John L. Fuller, Paul B. Sawin, Emil Fredericson, Mary Alexander, and a staff of scientific assistants and research fellows from various universities.

Eta Kappa Nu Association, national honorary organization of electrical engineers, elected three Eminent Members to the association on January 30. The scientists chosen were **Vannevar Bush,** president of the Carnegie Institution of Washington, **Royal W. Sorensen,** professor of electrical engineering at the California Institute of Technology, and **V. K. Zworykin,** head of research for the Radio Corporation of America. It was the first time

that Eta Kappa Nu had awarded this honor, although it has been provided for in the society's constitution for many years.

The ninth annual award of the Chicago Dental Society has been given to M. S. Burstone, instructor in pathology, Washington University School of Dentistry and Washington University School of Medicine. Dr. Burstone was cited for his work dealing with the effect of internal administration of radioactive phosphorus upon the development of the teeth and mandibular joint of the mouse. The award is made annually for an original investigation which contains some new material of value to dentistry.

The $1,000 Fisher Award in Analytical Chemistry will be presented to I. M. Kolthoff on March 28 at the Houston, Texas, session of the American Chemical Society's national meeting. Dr. Kolthoff, who is head of the Analytical Chemistry Division at the University of Minnesota, will be the third winner of the Fisher Award, established in 1947 to recognize and encourage outstanding achievement in the science of analytical chemistry. The first award was conferred on N. Howell Furman, professor of analytical chemistry, Princeton University; last year it was presented to G. E. F. Lundell, retired chief of the Chemistry Division of the National Bureau of Standards.

Fellowships and Prizes

The American Genetics Association is offering a thousand-dollar prize for the best essay written during 1950 in partial answer to the question: "Who marries whom, and why?" It is hoped that the contest will clarify some of the social, economic, and educational factors important in the determination of marriage choices. The purpose of the contest is to develop criteria for recognizing nongeographic factors which limit marriage choices.

An additional thousand dollars is offered in secondary prizes. The contest closes February 28, 1951. Competition is open to all qualified students and specialists in genetics. For additional information write to the American Genetic Association, 1507 M Street, N.W., Washington 5, D. C.

The Department of Chemistry of the School of Biological Sciences, University of Tennessee, is accepting applications for graduate teaching fellowships for the academic year 1950–51. The fellowships are open to students who will be candidates for the master's degree or the doctorate in biochemistry. Appointments are for 10 months and are renewable. First-year stipends are $1,000 for fellows holding the bachelor's degree and $1,500 for fellows holding the master's degree. Tuition fees are remitted. Applications, including transcript of college work, personal data, and a recent photograph, should be sent to the Dean of the School of Biological Sciences, University of Tennessee, Memphis, by *April 1*.

The 1950–51 Frank B. Jewett postdoctoral fellowships for research in the physical sciences have been awarded to James Bruce French, physicist, Massachusetts Institute of Technology; Ilse Lisl Novak, mathematician, Wellesley College; Robert Frank Steiner, chemist, Harvard University; David Emerson Mann, physicist, University of Minnesota; and Roy J. Glauber, physicist, Institute for Advanced Study. The fellowships grant $3,000 to the recipient and $1,500 to the institution at which he chooses to do his research.

The Committee for Research in Problems of Sex of the National Research Council expects to have a few thousand dollars available for new grants-in-aid during the fiscal period July 1, 1950 to June 30, 1951. Applications will be received until *March 15, 1950*. Blanks may be obtained from the Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C. Preliminary inquiries should be addressed to Dr. George W. Corner, Chairman of the Committee.

A fellowship in gynecological endocrinology will be available in the Department of Obstetrics and Gynecology, Jefferson Medical College and Hospital, on July 1. Applicants must have had at least a one year's residency or equivalent training in obstetrics and gynecology. Work will be done under the supervision of A. E. Rakoff, clinical professor of obstetrics and gynecological endocrinology. The yearly stipend is $1,800. For further details write to Lewis C. Scheffey, Head of Department of Gynecology, Jefferson Medical College and Hospital, Philadelphia 7.

Meetings and Elections

The National Academy of Sciences will hold its annual meeting April 24–26 in Washington, D. C. Sessions for the presentation of scientific papers will be held on Monday and Wednesday, April 24 and 26. Members wishing to submit papers or to introduce a paper by a nonmember should submit title and abstract (in duplicate) to the Home Secretary, 2101 Constitution Avenue, N.W. Washington, D. C. not later than *March 20*. A public lecture by I. I. Rabi, of Columbia University, will be given at 8:00 p.m. April 24 in the Academy Auditorium. The title of his address will be announced later. Headquarters for the meeting will be the Washington Hotel, 15th Street and Pennsylvania Avenue, Washington 4, D. C. Reservations may be made by writing directly to the hotel.

The American Physical Society will hold its 299th meeting in Washington, D. C. April 27–29. Titles and abstracts of all papers contributed for presentation should be received by Karl K. Darrow, Secretary, American Physical Society, Columbia University, New York City 27, by *March 3*.

The American Mathematical Society will hold its 454th meeting at Michigan State College, East Lansing, February 24–25 in Room 118 of the Physics-Mathematics Building. On Saturday morning, February 25, a joint session with the Industrial Mathematics Society will take place. The society's 455th meeting will be held at Columbia University, New

York City on Saturday afternoon, February 25. All sessions will take place in Room 301 of the Pupin Physics Laboratories. At 2:00 p.m. C. L. Siegel, of the Institute for Advanced Study, will speak on "Classes of Analytic Transformations."

The New School for Social Research, New York City, is presenting a series of 24 lectures on **"Frontiers of Research in Science and Medicine,"** which began February 7 and will run through May 23. The series is offered without fee by the New School and the Institute for Muscle Research. Among the scientists taking part are Albert Szent Györgyi, in charge of research at the Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Massachusetts; Otto Warburg, director, Kaiser Wilhelm Institute, Berlin-Dahlem; and Harry Goldblatt, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles.

The lectures are based on laboratory findings of the working scientists in medicine and its border fields in science and are designed to educate the layman in problems, methods, and achievements of modern scientific investigations. Current problems in chemistry and biochemistry, biophysics, and medicine are subjects of discussion.

The American Society of Naturalists elected the following officers at its 35th annual meeting: president, Th. Dobzhansky, Columbia University; vice president, H. H. Plough, Amherst College; secretary, Bentley Glass, Johns Hopkins University. D. P. Costello continues in office as treasurer.

A joint committee on agricultural services to foreign areas has been created by the Association of Land-Grant Colleges and Universities and the U. S. Department of Agriculture to assist in formulating plans to further the U. S. program of international cooperation in technical agriculture. The committee will also be concerned with the exchange of agricultural specialists and students with foreign countries.

Representatives of the association on the committee are John A. Hannah, president of Michigan State College; Charles E. Friley, president of Iowa State College; C. B. Hutchison, dean of agriculture and vice president of the University of California; H. P. Rusk, dean of the University of Illinois; Harry Brown, dean of the University of Georgia; and W. I. Myers, dean of Cornell University. Representing the department are Stanley Andrews, director, Office of Foreign Agricultural Relations; P. V. Cardon, administrator, Agricultural Research Administration; F. F. Elliott, associate chief, Bureau of Agricultural Economics; A. Rex Johnson, assistant director, Office of Foreign Agricultural Relations; T. Roy Reid, director, Office of Personnel; and M. L. Wilson, director of extension.

The annual spring meeting of the **Georgia Entomological Society** will be held in the American Legion Clubhouse at Fort Valley, Georgia, on March 3 and 4.

Horticultural Color Chart. Substantial progress was made towards a uniform standard for the biological sciences and horticultural groups at a meeting held on January 18 at the Chicago Natural History Museum. Although called primarily to discuss the needs of specialized plant societies, several representatives of the biological sciences were present, including Wendell H. Camp, president of the American Society of Plant Taxonomists, Theodore Just of the Museum staff, and Donald Wyman of the Arnold Arboretum.

The program for a scientific, accurate color chart began at Cornell University in October 1947, when the Commission on Testing and Reporting of the American Horticultural Council reported that without such a standard its work was meaningless. After an examination of existing standards, it was determined that all failed in some respect to meet the specifications set up, which included:

1. Low cost of reproduction, making wide distribution possible.
2. Relatively nonfading colors for permanence.
3. Color measurement by modern scientific color instruments for permanent recording.
4. Uniformly spaced samples in the color spectrum so that additional colors could be interspersed as needed.
5. Large samples on the edge of the page, so arranged that two or more samples or specimens could be compared directly, under or over the sample.
6. Nomenclature understandable to lay as well as scientific workers.
7. A wide range of colors to serve the entire field of biological sciences, with removable samples to limit range where desirable.
8. Both mat and glossy surfaces.

Two circumstances favored the progress of a chart based on these specifications. The importation from abroad of a new electronically controlled color press, designed for printing color cards for the paint trade, was one. Since paint color cards are color systems in miniature, by extending the scope of the process to include the 1,500 color samples which now seem necessary, the printing of the proposed chart would be enormously simplified. The press in question can print as many as 66 colors on a single sheet, and these colors need not be in any way related. For example, completely unrelated colors can be applied to a single sheet, each with individual texture and reflective surface. This press has perhaps a higher color accuracy than any color-reproducing process heretofore available, and it has been used to reproduce highly important color standards for governmental agencies. It is of no use for illustration reproduction, but is strictly a color-sampling press. Costs on this press would be roughly one-fifth of those for hand-pasted samples, the most accurate system heretofore available.

The second fortunate circumstance was the discovery that Dorothy Nickerson, color authority of the Production and Marketing Administration, U. S. Department of Agriculture, had for several years been gathering material for a horticultural color chart, and had been cooperating with workers in this field in gathering color data. As secretary of the Inter-Society Color Council, Miss Nickerson knew the need and had anticipated the call for scientific data.

Out of this work came dummies for proposed systems, meeting fully the specifications set up. These were based on data supplied Miss Nickerson by organizations affiliated with the American Horticultural Council and others.

At the Chicago meeting, the format suggested was approved, and the color range checked. Except for the addition of an additional red-yellow-yellow group and a blue-blue-red group, with higher-keyed colors in all groups, the colors were pronounced satisfactory.

Nomenclature will be decided by a committee, but the consensus of the meeting was that the Inter-Society Color Council names be adopted, with cross-indexing of Ridgway's Maerz & Paul, and other color system names. Scientists present at the meeting emphasized the importance of using names for which Latin equivalents are available, for permanent taxonomic records.

Recommendations of the meeting were sent to the American Institute of Biological Sciences for further action, which body has under consideration the appointment of a committee to carry the chart through to completion. Biologists interested in the use of color may still register their special needs by sending data on systems used, the colors most used in these systems, sections which need extension, etc., to Miss Dorothy Nickerson, Box 155, Benjamin Franklin Station, Washington, D. C., to Dr. M. O. Lee, Chairman, American Institute of Biological Sciences, National Research Council, Washington, D. C., or to me, as chairman of the committee.

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Miscellaneous

Two statements by scientific groups were made last week concerning the hydrogen bomb: one by the Federation of American Scientists in Washington, D. C., the other by a group of 12 physicists at the annual New York meeting of the American Physical Society at Columbia University. Both were based on President Truman's recent decision that the U. S. should go ahead with the construction of the hydrogen bomb. Both statements emphasized that there can be no security based on monopoly of a super weapon.

Excerpts from the FAS statement follow:

. . . No nation is secure against the hydrogen bomb. . . . American scientists are of many minds on many issues, but on one we unite: our country must turn from the false security of bombs to the slow, difficult task of gaining security by a positive approach to peace by mutual agreement, to peace by gradual disarmament, to peace by world-wide economic reconstruction and development.

The policy of our country has faced in two directions. We have sought to achieve international control of atomic energy on the one hand, while basing our military planning on atomic armaments. The question which faces us today is whether the United States will persist in its avowed policy of seeking peace through agreement or whether it will pay lip service to this policy while relying on force.

The decision on the hydrogen bomb can be interpreted by the world as a symbol that we have now set our course. We have placed a terrible weight in the balance for destruction. A greater weight must now be placed on the side of real security and peace.

Already a few voices have solemnly and wisely urged such a course. We repeat now our request that the President establish without delay a new commission with the broad perspective of the Acheson-Lilienthal Commission of 1946 to examine the whole issue of our atomic policy and to make a fresh start, a far-going revision which offers some real hope of breaking the present stubborn deadlock. . . . Our objective must continue to be effective atomic control, including thoroughgoing inspection. But we must consider alternative proposals, perhaps proposals without the far-reaching international ownership concept, perhaps proposals making greater concessions to national interests, certainly proposals in which procedural issues like the veto are subordinate to the simple question of adequacy in giving nations warning of possible violation.

We call on Americans to see in the President's announcement a new warning and a new challenge. We still have hope that there are no differences so great that they can only be solved by atomic war.

The 12 physicists, led by Hans A. Bethe, of Cornell, said in part:

. . . a hydrogen bomb, if it can be made, would be capable of developing a power 1,000 times greater than the present atomic bomb. New York, or any other of the greatest cities of the world, could be destroyed by a single hydrogen bomb.

We believe that no nation has the right to use such a bomb, no matter how righteous its cause. This bomb is no longer a weapon of war, but a means of extermination of whole populations. Its use would be a betrayal of all standards of morality and of Christian civilization. . . .

Statements in the press have given the power of the H-bomb as between two and 1,000 times that of the present fission bomb. Actually the thermonuclear reaction on which the H-bomb is based is limited in its power only by the amount of hydrogen which can be carried in the bomb. . . .

To create such an ever present peril for all the nations in the world is against the vital interests of both Russia and the United States. Three prominent Senators have called for renewed efforts to eliminate this weapon, and other weapons of mass destruction from the arsenals of all nations. Such efforts should be made, and made in all sincerity from both sides.

In the meantime, we urge that the United States, through its elected government, make a solemn declaration that we shall never use this bomb first. The only circumstance which might force us to use it would be if we or our allies were attacked by this bomb. There can be only one justification for our development of the hydrogen bomb, and that is to prevent its use.

The signers were: *S. K. Allison,* director of Insitute for Nuclear Studies, University of Chicago; *K. T. Bainbridge,* Harvard University; *H. A. Bethe,* Cornell University; *R. B. Brode,* University of California; *C. C. Lauritsen,* director of Kellogg Radiation Laboratory, California Institute of Technology; *F. W. Loomis,* chairman of Physics Department, University of Illinois; *G. B. Pegram,* dean of Graduate Faculties, Columbia University; *B. Rossi,* Massachusetts Institute of Technology; *F. Seitz,* University of Illinois; *M. A. Tuve,* director, Department of Terrestrial Magnetism, Carnegie Institution, Washington; *V. F. Weisskopf,* Massachusetts Institute of Technology; and *M. G. White,* Princeton University.

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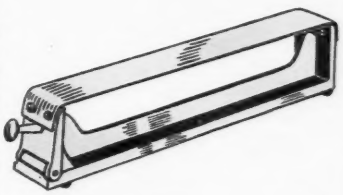

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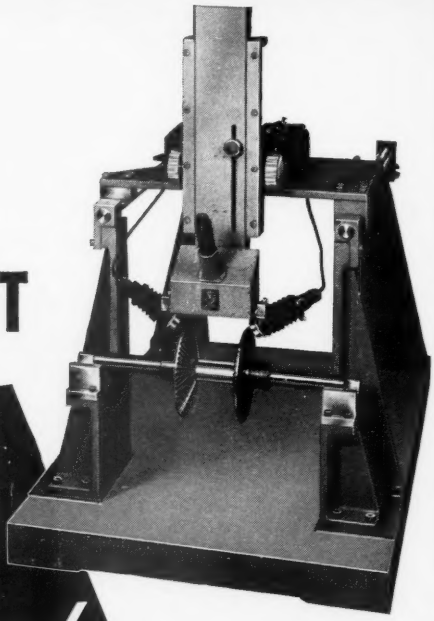

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